08/913,960

9200/1614

petition office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent 5,968,976	:	
Issued:	October 19, 1999	:	BOX: Patent Ext.
Inventors:	Barry A. MURRER, Nigel A. POWELL	:	
For:	PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES	:	
Assignee:	Shire International Licensing B.V.	:	

Mail Stop Patent Ext.
Commissioner of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF TERM UNDER 35 U.S.C. §156

SIR:

Applicant, Shire International Licensing B.V., a corporation organized and existing under and by virtue of the laws of The Netherlands, and having a principal place of business at Fred. Roeskestraat 123 Olympic Plaza, 1076EE, Amsterdam, The Netherlands, represents that it is the assignee of the entire interest in and to United States Letters Patent No. 5,968,976 granted to Barry A. Murrer and Nigel A. Powell on October 19, 1999, for "Pharmaceutical Composition Containing Selected Lanthanum Carbonate Hydrates". An assignment of said patent from the inventors was previously executed in the name of AnorMed Inc. and was recorded in the U.S. Patent and Trademark Office (PTO) at Reel 009638/ Frame 0749; a subsequent assignment of said patent was executed by AnorMed, Inc. in favor of Shire International Licensing B.V. on December 1, 2004 and was recorded in the PTO at Reel 015469/0166. A copy of this assignment is enclosed as Attachment A.

The active ingredient of FOSRENOL™ is lanthanum carbonate hydrate of the formula $La_2(CO_3)_3xH_2O$, wherein x is on average 4.5, which falls within the ambit of the claims of

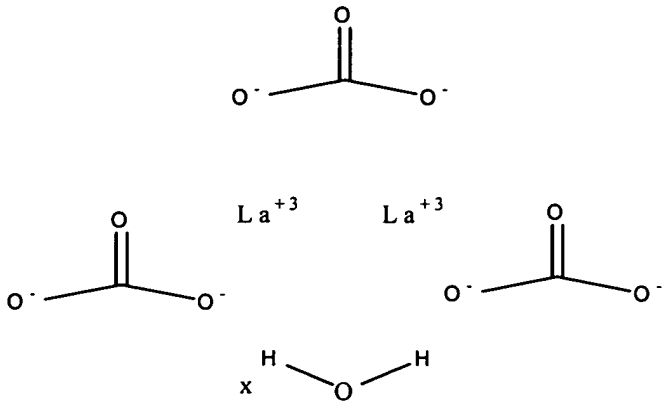
U.S. Patent 5,968,976.

Shire Development Inc. (Marketing Applicant) has been granted approval of its New Drug Application (NDA) by the Food and Drug Administration (FDA) for commercial marketing or use of FOSRENOL™. Shire International Licensing B.V. and Shire Development Inc. are both wholly owned subsidiaries of Shire Pharmaceuticals Group Plc. A power of attorney to the undersigned executed by Ms. Shona S. McDiarmid, is attached as Exhibit B. A corporate resolution by Shire International Licensing B.V., authorizing Ms. McDiarmid to act as a representative of and on behalf of Shire International Licensing B.V. in connection with all patent matters is attached as Exhibit C. The undersigned has thus been authorized to act on behalf of Shire International Licensing B.V., the assignee of Letters Patent No. 5,968,976.

Applicant, acting through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. §156 by providing the following information required by the rules promulgated by the PTO (37 C.F.R. §1.7100 - 1.785). For the convenience of the PTO, the information presented in this application is in a format which follows the requirements of 37 C.F.R. §1.740.

(1) **A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.**

The approved product, FOSRENOL™, is a chewable tablet formulation containing, as the active ingredient, lanthanum carbonate hydrate. The lanthanum carbonate hydrate has the formula: $La_2(CO_3)_3 \cdot xH_2O$, wherein x is on average 4.5. Lanthanum carbonate hydrate can be represented by the following structural formula:



where x is on average 4.5

Lanthanum carbonate hydrate has the CAS registry number **54451-24-0**.

(2) **A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.**

The approved product, FOSRENOL™, was subject to regulatory review under the Federal Food, Drug and Cosmetic Act Section 505 (21 U.S.C. §355).

(3) **An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.**

The approved product, FOSRENOL™, received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355) on October 26, 2004 (NDA-21-468).

(4) **In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in**

combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The only active ingredient in FOSRENOL™ is lanthanum carbonate hydrate ($La_2(CO_3)_3 \cdot xH_2O$, wherein x is on average 4.5). The active ingredient has not been previously approved for commercial marketing or use under Section 505 or any other section of the Federal Food, Drug and Cosmetic Act prior to its approval in NDA-21-468 by the FDA. It has not been approved for commercial marketing or use under the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) **A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.**

This application for extension of patent term under 35 U.S.C. 156 is being submitted within the permitted 60 day period pursuant to 37 C.F.R. §1.720(f), which period will expire December 25, 2004.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

The complete identification of the patent for which extension is being sought is as follows:

Inventors:	Barry A. Murrer and Nigel A. Powell
Patent Number:	5,968,976
Issue Date:	October 19, 1999
Expiration Date:	March 19, 2016

(7) **A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.**

See Attachment D for a complete copy of the patent identified in paragraph (6) hereof.

(8) **A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.**

No certificate of correction or re-examination certificate has been issued with regard to U.S. Patent 5,968,976. No disclaimer has been filed in US 5,968,976. Enclosed at Attachment E is a copy of the Maintenance Fee Statement which shows that the maintenance fee for year four has been paid.

(9) **A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:**

(i) **The approved product, if the listed claims include any claim to the approved product;**

(ii) **The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and**

(iii) **The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.**

U.S. Patent 5,968,976 claims the approved product FOSRENOL™ and methods of using and manufacturing the approved product. Specifically, compositions containing the active ingredient lanthanum carbonate hydrate ($La_2(CO_3)_3 \cdot xH_2O$, wherein x is on average 4.5) and methods of using such compositions are covered under claims 1-4 and 7-10 which follow:

1. A pharmaceutical composition for the treatment of hyperphosphataemia comprising lanthanum carbonate of the formula

$$La_2(CO_3)_3 \cdot xH_2O$$

where x has a value from 3 to 6, in admixture with a pharmaceutically acceptable diluent or carrier in a form for administration to the gastrointestinal tract.

2. A composition according to claim 1, wherein x has a value from 3.5 to 5.

3. A composition according to claim 2, wherein x has a value from 3.8 to 4.5.

4. A composition according to any one of claims 1 to 3 in unit dosage form to provide from 0.1 to 20 g/day.

7. A method to treat hyperphosphataemia in a subject which method comprises administering to said subject an amount of lanthanum carbonate of the formula

$$La_2(CO_3)_3 \cdot xH_2O$$

wherein x has a value from 3 to 6 effective to treat said hyperphosphataemia.

8. The method of claim 7 wherein x has a value from 3.5 to 5.

9. The method of claim 8 wherein x has a value from 3.8 to 4.5.

10. The method of any of claims 7-9 wherein said administering is by an oral route.

(i) Claims 1-4 of the patent read on the approved product. Thus, the approved product incorporates lanthanum carbonate hydrate ($La_2(CO_3)_3 \cdot xH_2O$, wherein x is on average 4.5) in admixture with a pharmaceutically acceptable diluent or carrier in a form for administration to the gastrointestinal tract (claim 1). Further, x (as defined above) has a value from 3.5 to 5 (claim 2), and a value from 3.8 to 4.5 (claim 3).

Still further, the unit dosage forms of FOSRENOL™ are 250 mg or 500 mg tablets as elemental Lanthanum, which corresponds to 0.0018 or 0.0036 moles of ($La_2(CO_3)_3xH_2O$, wherein x is on average 4.5). The molecular weight of FOSRENOL™ is 457.8 g. Thus, each

tablet provides 0.82g or 1.65g of $La_2(CO_3)_3xH_2O$, wherein x is on average 4.5. Thus, claim 4 reads on FOSRENOL™.

(ii) Claims 7-10 of the patent read on the method of using the approved product. Thus, FOSRENOL™ is used to treat hyperphosphataemia in a subject (claims 7-9) and is administered by an oral route (claim 10).

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) application or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued;

....

The relevant dates and information pursuant to 35 U.S.C. §156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i)(A) The Investigational New Drug Application (IND-55,054) for lanthanum carbonate hydrate was filed January 14, 1998 and became effective on **February 13, 1998.**

(B) The New Drug Application (NDA-21-468) for FOSRENOL™ was initially submitted to the FDA on April 30, 2002, and

(C) the New Drug Application was approved on October 26, 2004.

(11) **A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.**

A brief description of the significant activities undertaken by marketing applicant during the applicable regulatory review period is attached hereto as Attachment F and is a chronological synopsis of the major communications between Applicant and the FDA from **July 7, 1997 to October 20, 2004.**

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined;

Applicant is of the opinion that U.S. Patent 5,968,976 is eligible for extension under 35 U.S.C. §156 because it satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C. §156(a); 37 C.F.R. §1.720(a)

U.S. Patent 5,968,976 claims (i) a product, and (ii) a method of using a product, as defined in 37 C.F.R. § 1.710(a).

(b) 35 U.S.C. §156(a)(1); 37 C.F.R. §1.720(g)

The term of U.S. Patent 5,968,976 has not expired before submission of this application, which is believed to be in compliance with 37 CFR § 1.741;

(c) 35 U.S.C. §156(a)(2); 37 C.F.R. §1.720(b)

The term of U.S. Patent 5,968,976 has never been extended under 35 U.S.C. § 156(e)(1);

(d) 35 U.S.C. §156(a)(3); 37 C.F.R. §1.730

The application for extension is submitted by a registered practitioner on behalf of the owner of record in accordance with the requirement of 35 U.S.C. §156(d) and the rules of the U.S. Patent and Trademark Office. Proof that the applicant is the owner of record is provided by a copy of the assignment of U.S. Pat. No. 5,968,976 executed by AnorMed Inc. in favor of Shire International Licensing B.V. on December 1, 2004, and submitted to the U.S. Patent and Trademark Office for recordation on December 16, 2004

(Attachment A). Proof that the registered practitioner is authorized to act on behalf of the patent owner is provided by a copy of the power of attorney, filed with the U.S. Patent and Trademark Office on December 21, 2004 in connection with U.S. Pat. No. 5,968,976 (Attachment B);

(e) 35 U.S.C. §156(a)(4); 37 C.F.R. §1.720(d)

The product FOSRENOL™ has been subject to a regulatory review period as defined in 35 U.S.C. §156(g) before its commercial marketing or use;

(f) 35 U.S.C. §156(a)(5)(A); 37 C.F.R. §1.720(e)(i)

The commercial marketing or use of the product FOSRENOL™ after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetics Act (21 U.S.C. § 360) under which such regulatory review period occurred.

(g) 35 U.S.C. §156(c)(4); 37 C.F.R. §1.720(h)

No other patent has been extended for the same regulatory review period for the product FOSRENOL™.

(h) 35 U.S.C. §156(d)(1); 37 C.F.R. §1.720(f)

The application is submitted within the permitted 60 day period beginning on the date the product first received permission for commercial marketing or use.

(i) The length of extension of the patent term of U.S. Patent 5,968,976 claimed by applicant is **951** days. The length of extension was determined pursuant to 35 U.S.C. § 156(g)(1) and 37 C.F.R. §1.775 (c) as follows:

(i) The regulatory review period under 35 U.S.C. §156(g)(1)(B) began **February 13, 1998** and ended **October 26, 2004**, a total

of **2447** days, which is the sum of (ii) and (iii) below;

(ii) The period of review under 35 U.S.C. §156(g)(1)(B)(i), the IND period, began on **February 13, 1998** and ended on **April 30, 2002,** which is **1537** days.

(iii) The period of review under 35 U.S.C. §156(g)(1)(B)(ii), the "Application Period," began on **April 30, 2002** and ended **October 26, 2004,** which is **910** days.

(j) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 12(i)(i) hereof (**2447** days) less

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (October 19, 1999), which is **613** days, and

(ii) **The number of days during which applicant did not act with due diligence, which is zero (0) days, and**

(iii) One-half the number of days determined in subparagraph 12(i)(ii) hereof (1537) after subtracting therefrom the number of days of subparagraphs (12)(j)(i) and (j)(ii) hereof (**613** days in total), or **462** days,

which totals **1372** days.

(k) The number of days as determined in subparagraph 12(j)(iii) hereof (**1372** days) when added to the original term of the patent would result in the date **December 21, 2019.**

(l) Fourteen (14 years) when added to the date of the NDA approval (**October 26, 2004**) would result in the date **October 26, 2018.**

(m) The earliest date as determined in paragraphs 12(k) and 12(l) is **October 26, 2018.**

(n) The issuance of the original exemption occurred after September 24, 1984. Five (5) years when added to the original expiration date of the patent (**March 19, 2016**) would result in the date **March 19, 2021.**

(o) The earlier date as determined in paragraphs (m) and (n) is **October 26, 2018.** The patent is currently set to expire on March 19, 2016. Therefore, the length

of extension of patent term claimed by applicant is **951 days or 2 years and 221 days.**

(13) **A statement that the Applicant acknowledges a duty to disclose to the Director of the U.S. Patent and Trademark Office and to the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.**

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any Information which is material to the determination of entitlement to the extension sought.

(14) **Prescribed Fee:**

The prescribed fee pursuant to 37 C.F.R. §1.20(j) for receiving and acting upon this application is to be charged to the Deposit Account of Applicant as authorized in the attached letter, which is submitted in triplicate.

(15) **The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed**

Marc. S. Gross
DARBY & DARBY P.C.
P.O. Box 5257
New York, 10150-5257
(212) 527-7700
(212) 753-6237 (Fax)

Four copies of these application papers, certified as such, are being submitted herewith, in compliance with 37 C.F.R. § 1.740(b) and as suggested by MPEP § 2753.

Respectfully submitted,

Marc S. Gross
Reg. No. 19,614
Attorney for Applicant

DARBY & DARBY P.C.
Post Office Box 5257
New York, NY 10150-5257
212-527-7700

Attachment List

Attachment A -- Assignment of U.S. Patent No. 5,968,976 from AnorMed, Inc. in favor of Shire International Licensing B.V., executed December 1, 2004, recorded at Reel/Frame 015469/0166.

Attachment B -- Power of Attorney, signed by Shona McDiarmid, on behalf of Shire Pharmaceuticals Group Plc, and Statement Under 37 C.F.R. § 1.73(b).

Attachment C -- Statement authorizing Shona McDiarmid to act on behalf of Shire International Licensing B.V.

Attachment D -- Copy of U.S. Letters Patent No. 5,968,976

Attachment E -- Maintenance Fee Statement for U.S. Letters Patent No. 5,968,976

Attachment F -- Chronological synopsis of the major communications between Applicant and the FDA

A

CONFIRMATORY ASSIGNMENT

WHEREAS,

AnorMED Inc., a company incorporated in Canada whose principal place of business is #200 - 20353 64th Avenue, Langley, B.C. Canada V2Y 1N5, hereinafter referred to as the ASSIGNOR, is the current owner of the entire right, title and interest in and to the following U.S. Letters Patent and/or U.S. applications, the inventions covered thereby, the application(s) from which said Letters Patent issued and all U.S. and foreign and international treaty priority rights claimed therein or corresponding thereto:

U.S. Patent	**Reel/Frame**
No. 5,968,976	**009638/0749**

as well as all continuation and divisional applications claiming benefit of any of said applications,

AND WHEREAS,

Shire International Licensing B.V., of Fred. Roeskestraat 123 Olympic Plaza, 1076EE, Amsterdam, The Netherlands, hereinafter referred to as ASSIGNEE, is desirous of acquiring the entire right, title and interest in and to said inventions, said Letters Patent including any and all renewals, reissues and prolongations thereof, and said applications, including the right to sue under said Letters Patent and applications for infringement occurring herebefore.

AND WHEREAS,

ASSIGNOR has entered into an Assignment as of 1 December, 2004 with ASSIGNEE regarding said Letters Patent.

NOW, THIS WITNESSETH that for good and valuable consideration, the receipt whereof is hereby acknowledged, ASSIGNOR hereby assigns, sells and transfers to ASSIGNEE, its assigns and legal representatives, the entire and exclusive right, title and interest in and to said inventions, said Letters Patent including any and all renewals, reissues and prolongations thereof, and said applications, including the right to sue under said Letters Patents and applications, for infringement occurring herebefore, ASSIGNEE and its assigns and legal representatives to have, hold, exercise, and enjoy said inventions, Letters Patent including any

and all renewals, reissues, and prolongations thereof, and said applications, with all the rights, powers, privileges, and advantages in anywise arising from or appertaining thereto, for and during the term or terms of said Letters Patent and any future patents issuing from said applications, including any and all renewals, reissues, and prolongations thereof, for the use and benefit of ASSIGNEE and its assigns and legal representatives, in as ample and beneficial a manner to all intents and purposes as the ASSIGNOR might or could have held and enjoyed the same, if this assignment had not been made.

AnorMED Inc.

Date: 1 December, 2004

By: 

Name: **Michael J. Abrams**

Title: President and CEO

B

PTO/SB/81 (11-04)
Approved for use through 11/30/2005. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM

Application Number	08/913,960 (U.S. 5,968,976)
Filing Date	January 2, 1998
First Named Inventor	Barry A. MURRER
Title	Pharmaceutical Composition Containing Selected Lanthanum Carbonate Hydrates
Art Unit	1614
Examiner Name	D. C. Jones
Attorney Docket No.	020342/8200926

I hereby revoke all previous powers of attorney given in the above-identified application.

I hereby appoint:

[X] Practitioners associated with the Customer Number: 07278

OR

[ ] Practitioner(s) named below:

Name	Registration Number	Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please recognize or change the correspondence address for the above-identified application to:

[X] The address associated with the above-mentioned Customer Number:

OR

[ ] The address associated with Customer Number:

OR

[ ] Firm or Individual Name: Marc S. Gross, DARBY & DARBY P.C.

Address	P.O. Box 5257				
City	New York	State	NY	Zip	10150-5257
Country	US	Telephone	(212) 527-7700	Fax	(212) 753-6237

I am the:

[ ] Applicant/Inventor.

[X] Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Signature		Date	December 15, 2004
Name	Shona S. McDiarmid	Telephone	514-787-2320
Title and Company	Vice President Global Intellectual Property, Shire Pharmaceuticals Group plc		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[ ] *Total of 1 forms are submitted.

Express Mail Label No. Dated: _____

PTO/SB/96 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Shire International Licensing B.V.

Application No./Patent No.: 5,968,976 Filed/Issue Date: October 19, 1999

Entitled: PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES

Shire International Licensing B.V. (Name of Assignee) , a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. [x] the assignee of the entire right, title, and interest; or

2. [ ] an assignee of less than the entire right, title and interest.
The extent (by percentage) of its ownership interest is _____ %

in the patent application/patent identified above by virtue of either:

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. [x] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From: MURRER, Barry Anthony and POWELL, Nigel Anthony To: Johnson Matthey P.L.C.
The document was recorded in the United States Patent and Trademark Office at
Reel 8946, Frame 0746.

2. From: Johnson Matthey P.L.C. To: AnorMed Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 9638, Frame 0749.

3. From: AnorMed Inc. To: Shire International Licensing B.V.
A copy of this executed assignment is attached. It will be forwarded to the USPTO for recordation.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[x] Copies of assignments or other documents in the chain of title are attached.
[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature	December 15, 2004 Date
Shona S. McDiarmid Printed or Typed Name	514-787-2320 Telephone Number
Vice President, Global Intellectual Property Title	Shire Pharmaceuticals Group plc

Express Mail Label No.	Dated: _____

C.

Shire International Licensing BV
Olympic Plaza Fred. Roeskestraat 123
1076 EE Amsterdam PO Box 75032
1070 AA Amsterdam The Netherlands
Tel +31 (0) 20 577 1177 Fax +31 (0) 20 577 1188
http://www.shire.com

Shire

RESOLUTION

Whereas the Company wishes to authorise Shona McDiarmid, Vice-president Global Intellectual Property to execute and deliver for and on behalf of the Company, any documents, agreements or other instruments pertaining to any patent, trademark or copyright filing, prosecution, maintenance, defence or related issues, until such authority is revoked by resolution;

IT WAS RESOLVED:

PATENTS AND TRADEMARKS

1. THAT, until revoked by resolution, Shona McDiarmid, Vice-president Global Intellectual Property be authorised for and on behalf of the Company to execute and deliver any documents, agreements or other instruments pertaining to any patent, trademark or copyright filing, prosecution, maintenance, defence or related issues, as she in her discretion may approve, her approval of any such documents, agreements or instruments shall be conclusively evidenced by her execution and delivery of such documents, agreements or instruments.

2. THAT, until revoked by resolution, Shona McDiarmid, Vice-president Global Intellectual Property be authorized and directed to do all such acts and things and to execute or cause to be executed all such documents, agreements and other instruments as in such person's opinion may be necessary or desirable to complete the matters hereby approved and authorized.

Amsterdam, November 6, 2002

SHIRE INTERNATIONAL LICENSING B.V.

By:
Johan D. Evenens
Special Proxyholder

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US005968976A

United States Patent [19]

Murrer et al.

[11] Patent Number: 5,968,976

[45] Date of Patent: Oct. 19, 1999

[54] **PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES**

[75] Inventors: **Barry A Murrer; Nigel A Powell**, both of Berkshire, United Kingdom

[73] Assignee: **AnorMed Inc.**, Langley, Canada

[21] Appl. No.: **08/913,960**

[22] PCT Filed: **Mar. 19, 1996**

[86] PCT No.: **PCT/GB96/00575**

§ 371 Date: **Jan. 2, 1998**

§ 102(e) Date: **Jan. 2, 1998**

[87] PCT Pub. No.: **WO96/30029**

PCT Pub. Date: **Oct. 3, 1996**

[30] **Foreign Application Priority Data**

Mar. 25, 1995 [GB] United Kingdom 9506126

[51] **Int. Cl.**[6] **A01N 55/02**

[52] **U.S. Cl.** **514/492**; 514/512; 424/715; 534/16

[58] **Field of Search** 534/16; 514/492, 514/512; 424/715

[56] **References Cited**

PUBLICATIONS

Yanagihara et al., "Synthesis of Lanthanide Carbonates", Journal of the Less–Common Metals, 167(2) pp. 223–232, 1991.

Patent Abstract of vol. 11, No. 371, (C–462), Dec. 3, 1987 & JP, A, 62 145024 (Asahi Chem Ind Co Ltd), Jun 29, 1987.

Chemical Abstracts, vol. 107, No. 26, Dec. 28, 1987, abstract No. 249009, Mineely et al., "Molten potassium pyrosulfate: reactions of lanthanum metal and six of its compunds", XP002010788, see abstract, Aust. J. Chem. 40(7), pp. 1309–1314, 1987.

Chemical Abstracts, vol. 104, No. 26, Jun. 30, 1986, abstract No. 236218, Mzareulisvili et al., "Study of interaction of lanthanum nitrate with alkali metal and ammonium carbonates", XP002010789, Soobshch. Akad. Nauk Gruz. 121(1), pp. 81–84, (1986).

Chemical Abstracts, vol. 87, No. 20, Nov. 14, 1977, abstract No. 161013, Oda et al., "Studies on the crystal water of lanthanum carbonates", XP002010790, Oita Daigaku Kyoikygakubu Kenku Kiyo, Shizen Kagaku, 4(5), pp. 1–6, 1975.

Primary Examiner—Dwayne C. Jones

Attorney, Agent, or Firm—Morrison & Foerster, LLP

[57] **ABSTRACT**

Selected lanthanum carbonate hydrates may be administered into the gastrointestinal tract, to treat hyperphosphataemia in patients with renal failure.

10 Claims, 4 Drawing Sheets

Fig. 1

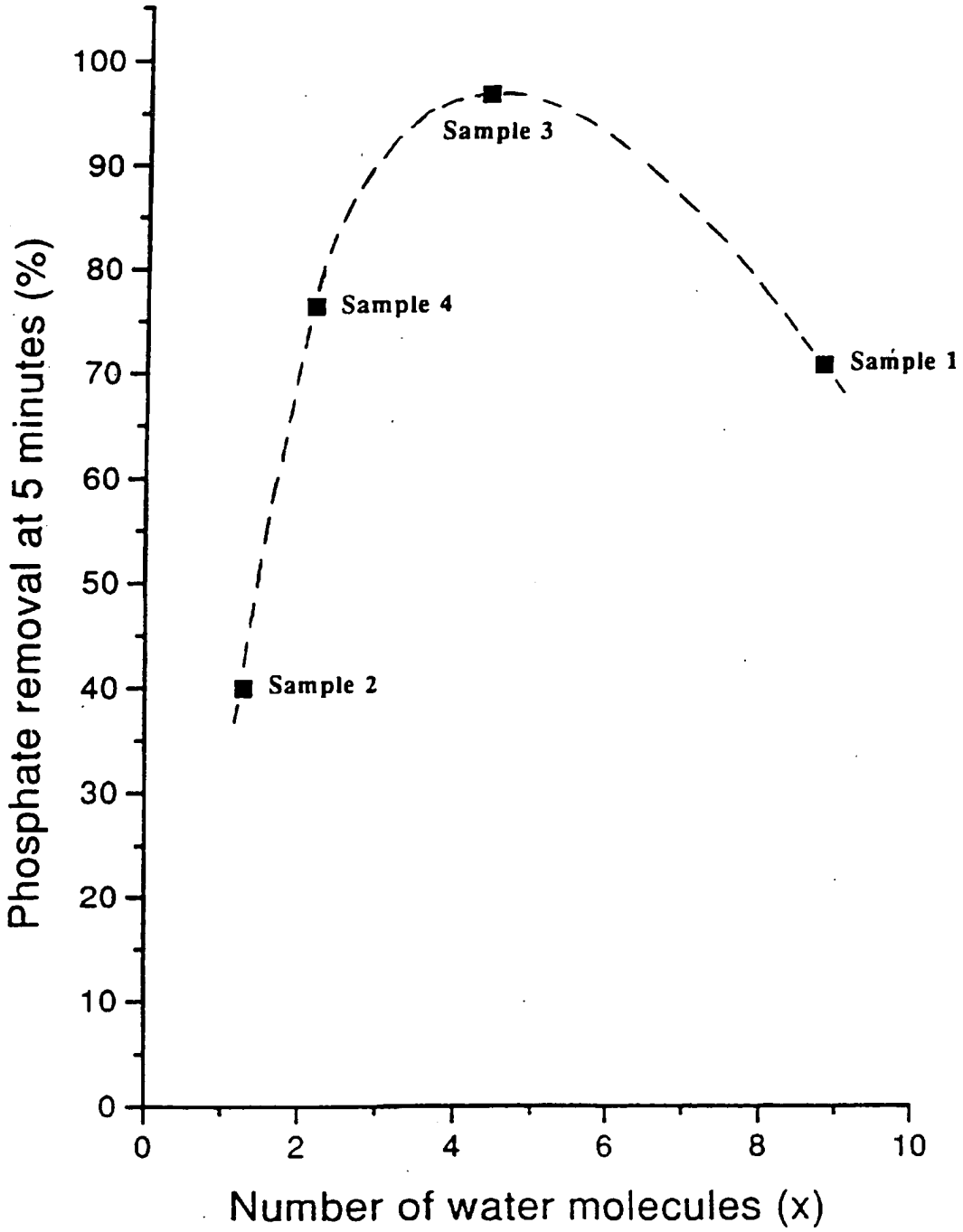

Phosphate removal at 5 minutes (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
Number of water molecules (x)
Sample 1
Sample 2
Sample 3
Sample 4

Fig. 2

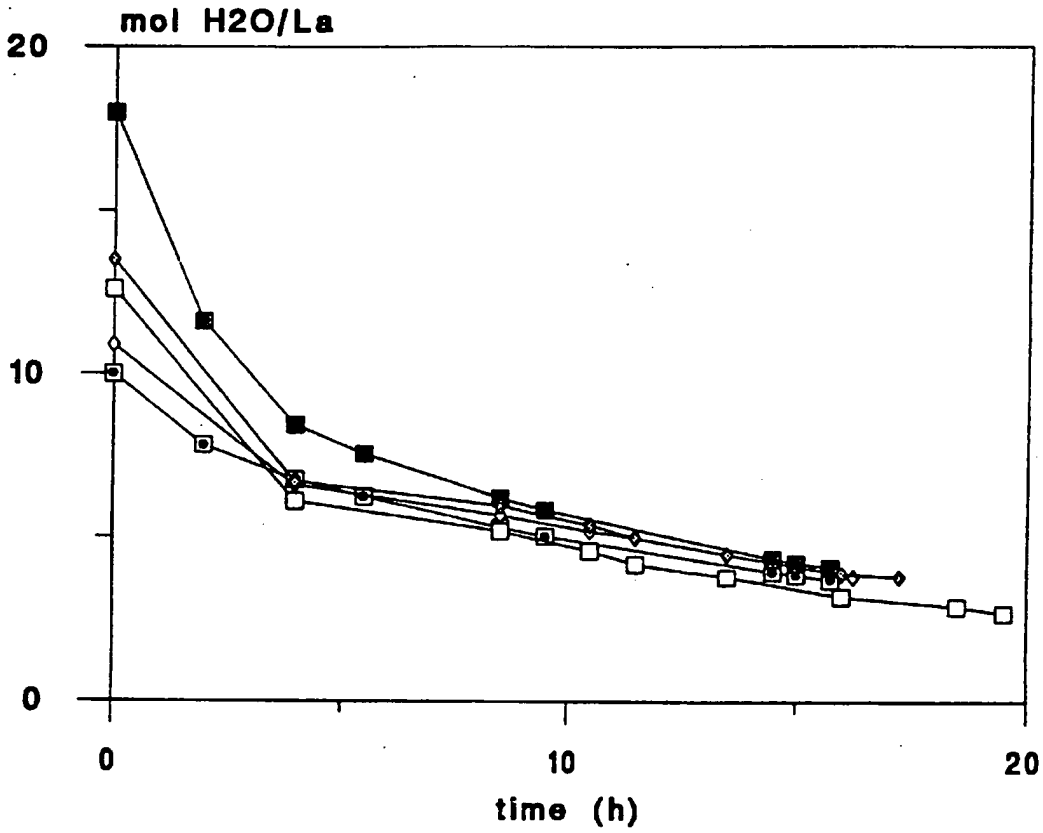


Fig. 3

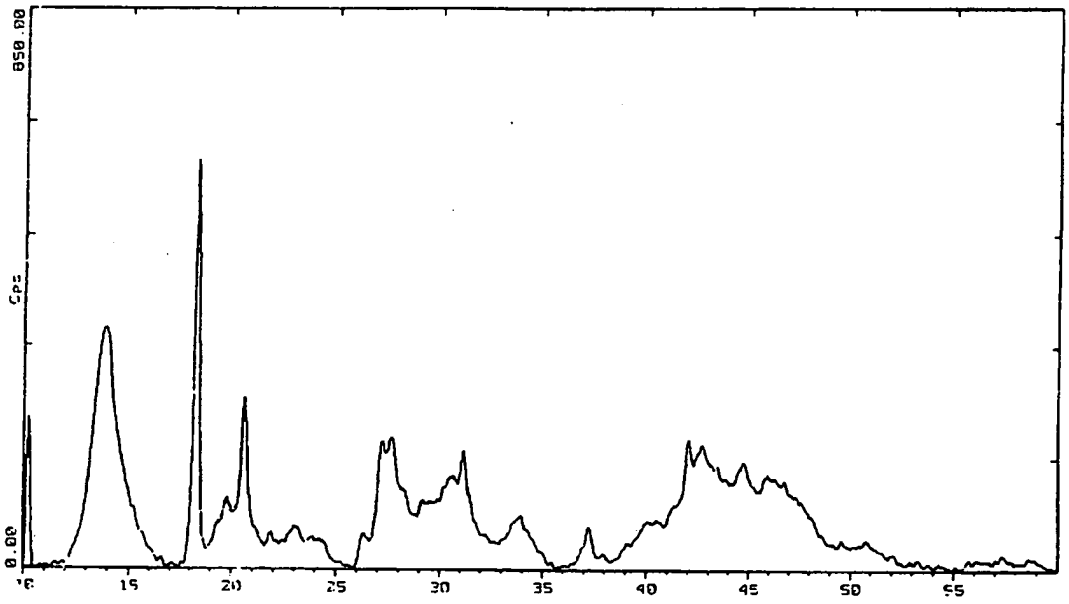
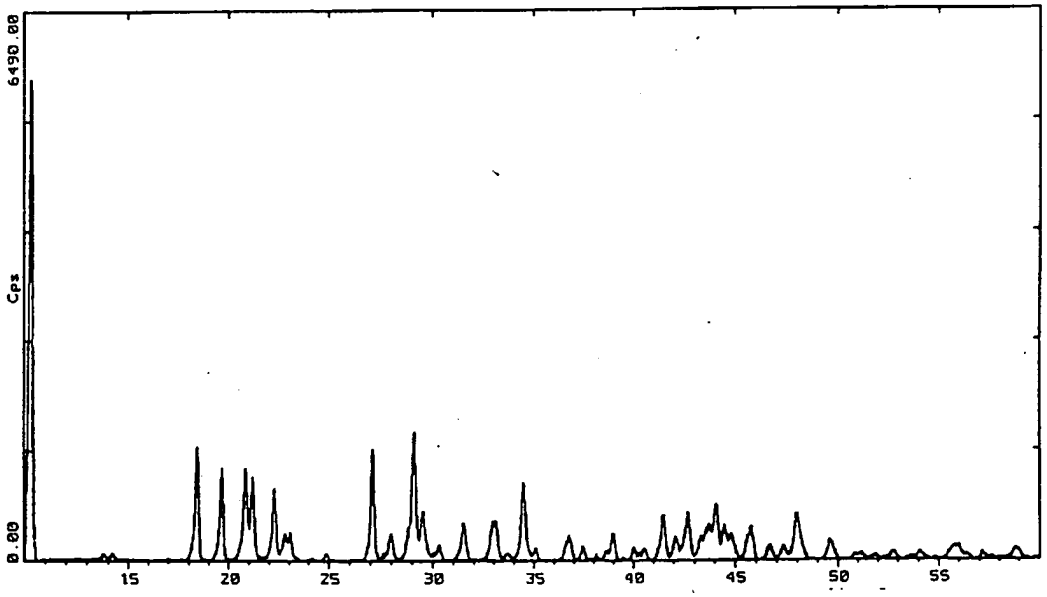


Fig.4



PHARMACEUTICAL COMPOSITION CONTAINING SELECTED LANTHANUM CARBONATE HYDRATES

This application is a 371 of PCT/GB96/00575 filed on Mar. 19, 1996.

This invention concerns a novel and inventive pharmaceutical composition and method, more particularly it concerns a composition for the treatment of hyperphosphataemia.

Hyperphosphataemia is a particular problem of patients with renal failure, using dialysis equipment. Conventional dialysis fails to reduce levels of phosphate in the blood, so that the levels rise in time. It is known to control phosphate levels by the oral administration of aluminium salts, or calcium salts. With the known toxic effects of aluminium, aluminium-based therapy tends to be avoided. In the case of calcium salts, calcium is absorbed rather readily from the gut, and in turn causes hypercalcaemia.

It has been suggested (Nakagawa et al, Trans Am Soc Intern Organs, 31, (1985) 155–9) that hydrous cerium oxide could be used as a bead in an ion-exchange column, to bind phosphate during dialysis. Japanese published patent application 61 004 529 appears to cover the same idea, suggesting that the hydrous oxides of La, Ce and Y may be used in the column. However, although the rare earths are generally considered of low toxicity according to the Hodge-Sterner classification system (Am Ind Hyg Assoc Quart, 10, (1943), 93), their toxicity when given iv, which corresponds to use in a blood dialysis system, is significant and we are not aware that the suggested ion exchange system or any development thereof has met with widespread acceptance or has been tested clinically for hyperphosphataemia.

It appears that cerium oxide or oxalate was administered many years ago for different medical indications, but that this has fallen into complete disuse.

Japanese published patent application number 62-145024 (Asahi Chemical Ind KK) discloses that rare earth carbonates, bicarbonates or organic acid compounds may be used as phosphate binding agents. One example of said published application relates to the use of lanthanum carbonate, although in the tests described, cerium organic acid salts and carbonate gave better phosphate ion extraction than lanthanum carbonate. Example 11 of said published application prepares $La_2(CO_3)_3.H_2O$, ie the monohydrate; all the other Examples are directed to rare earth carbonates other than lanthanum carbonate.

We have now discovered that certain forms of lanthanum carbonate exhibit improved performance in a variety of tests, over standard commercial lanthanum carbonate, which is believed to be the octahydrate form, and over $La_2(CO_3)_3.H_2O$ or similar compounds.

According to one aspect therefore, the present invention is the use of lanthanum carbonate of formula $La_2(CO_3)_3.xH_2O$ where x has a value from 3 to 6, preferably from 3.5 to 5, more especially from 3.8 to 4.5, for the preparation of a medicament for the treatment of hyperphosphataemia by administration into the gastrointestinal tract.

The invention further provides a pharmaceutical composition comprising said lanthanum carbonate, in admixture or association with a pharmaceutically acceptable diluent or carrier, in a form for administration into the gastrointestinal tract for the treatment of hyperphosphataemia.

The invention may also be expressed as a method of treatment of hyperphosphataemia in a patient with renal failure, comprising the administration of an effective dose of said lanthanum carbonate into the gastrointestinal tract.

According to another aspect, the present invention is a process for the preparation of lanthanum carbonate which comprises the steps of:

(i) reacting lanthanum oxide with an acid which gives a soluble salt of lanthanum;

(ii) reacting a solution of the thus obtained lanthanum salt with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and

(iii) controlled drying of the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

According to yet another aspect, the present invention is lanthanum carbonate when obtained by the above-mentioned process.

According to a further aspect, the present invention is lanthanum carbonate of the formula $La_2(CO_3)_3.xH_2O$ where x has a value from 3 to 6.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the present invention are described below, by way of example only, with reference to the accompanying drawings in which:

FIG. 1 illustrates the phosphate-binding capability of lanthanum carbonates having different degrees of water of crystallisation;

FIG. 2 illustrates the drying curves for five batches of lanthanum carbonate prepared by the method indicated in Example 1;

FIG. 3 illustrates the XRD analysis of lanthanum carbonate $4H_2O$ prepared by the method indicated in Example 2; and

FIG. 4 illustrates the XRD analysis of lanthanum carbonate $8.8H_2O$ of Sample 1 above.

For the tests described hereinafter, samples of lanthanum carbonate were obtained as follows:

Sample 1. Commercial lanthanum carbonate obtained from a chemical company.

This was characterised by elemental analysis (La, C, H), TGA, X-ray powder diffraction and ir spectroscopy, to have the formula $La_2(CO_3)_3.8.8H_2O$.

Samples 2–4 were prepared by heating portions of Sample 1 at varying temperatures for varying lengths of time, either under vacuum or at atmospheric pressure to obtain materials of formula $La_2(CO_3)_3.xH_2O$ where $0<x<8$.

Sample	Initial wt (g)	Temp (° C.)	Time (min)	Vacuum (Y/N)	Wt loss (g)	x
2	5.00	175	240	Y	1.09	1.3
3	20.0	80	180	N	2.6	4.4
4	5.01	100	720*	N	0.96	2.2

*Dried to constant weight.

Sample 5 is a sample of lanthanum carbonate which when analysed indicated a formula of $La(CO_3)_3.4H_2O$.

Sample 6 is a sample of lanthanum carbonate prepared according to Example 1 below and having the formula $La_2(CO_3)_3.3.8H_2O$.

In order to show that certain lanthanum carbonate hydrates are significantly different in phosphate binding activity from both lanthanum carbonate octahydrate and from $La_2(CO_3)_3.H_2O$, samples were tested as follows:

i) a stock solution was prepared by dissolving 13.75 g of anhydrous Na_2HPO_4, 8.5 g of NaCl in 1 litre deionised water.

ii) 100 ml of the stock solution was adjusted to pH3 by the addition of concentrated HCl.

iii) A 5 ml sample was taken and filtered through a 0.02 μm filter to give a Time 0 sample. This was analysed for phosphate using a Sigma Diagnostics Colorimetric Phosphorus test kit.

iv) 5 ml fresh stock solution was added to reestablish 100 ml, and the pH was re-adjusted to approximately 3.

v) $La_2(CO_3)3.xH_2O$ as a dry powder was added in an amount according to the molecular weight of the particular hydrate, to give a two-fold molar excess of lanthanum over phosphate and stirred at room temperature.

vi) Sampling was carried out at time intervals from 0.5 to 10 minutes, and the percentage of phosphate was determined as in iii) above. The results are shown in the Table 1 below.

TABLE 1

TIME	% PHOSPHATE REMOVED Sample					
(Minutes)	1	2	3	4	5	6
0						
0.5		13.4	18.8	15.1	22.9	31.4
1	29	18.4	31.5	26.8	40.4	55.5
1.5		25.4	43.1	36	55.2	74.8
2		28.1	50.6	45.3	69.5	88.1
2.5		30.8	60.5	51.8	79.9	95.3
3		34.4	69	57.6	90.3	99.6
4						100
5	70.5	39.9	96.5	76.3	100	100
10	100	ND	99.1	ND	100	100

It can readily be seen from Table 1 that Sample 3 ($La_2(CO_3)_3.4.4H_2O$); Sample 5 ($La_2(CO_3)_3.4H_2O$) and Sample 6 ($La_2(CO_3)_3.3.8H_2O$ appreciably quicker than the $8.8H_2O$, $.1.3H_2O$ or $2.2H_2O$ forms. We believe that the results for $La_2(CO_3)_3.1.3H_2O$ are in agreement with the results shown in the above mentioned Japanese published patent application number 62-145024 where for $La_2(CO_3)_3.H_2O$, only 90% removal is shown after 120 minutes.

It can also be readily seen from FIG. 1 of the accompanying drawings that the highest phosphate removal is obtained with lanthanum carbonates having 3 to 6 molecules of water.

The present invention offers the possibility of binding phosphate without any incursion of lanthanum into the blood stream, where toxic effects can cause problems. The specified lanthanum carbonate has negligible absorption from the gut, as shown by the in vivo tests described below.

Throughout this document, the term "treatment" is intended to include preventative treatment.

Processes for preparing lanthanum carbonates according to the present invention are described by way of illustration in the following Examples 1 and 2.

EXAMPLE 1

Lanthanum oxide (1.5 kg, 4.58 mol) was suspended in water (5.5 litres) in a 20 litre flask. Nitric acid (Analar grade, 69%, SG 1.42, 1.88 litres, 29.23 mol) was added to the stirred solution over 1.5 hours at such a rate as to keep the temperature between 60–80° C. The resulting lanthanum nitrate solution was left to cool to room temperature and filtered. A solution of sodium carbonate (1.65 kg, 15.57 mol) in water (7.75 litres) was added to the stirred lanthanum nitrate solution over 45 minutes. At the end of the addition the pH of the suspension w as 9.74. The suspension was left overnight, filtered (Buchner funnel, 540 paper) and dried on the filter in a current of air for 30 minutes. The solid was then re-suspended in water, stirred for 40 minutes and filtered. This procedure was repeated to give a total of six washes, when the nitrate concentration in the filtrate was <500 ppm. The final material (4.604 kg) was divided between three Pyrex dishes and a sample from each analysed for water content. (By decomposition of weighed sample of ($La_2(CO_3)_3.xH_2O$ at 1050° C., 2 hours to La_2O_3). The dishes were then placed in a fan oven at 80° C. and the weight loss of each dish monitored until the material of the required degree hydration was obtained. The progress of the drying is shown below

Time	mol H_2O/La		
(hours)	Dish 1	Dish 2	Dish 3
3.50	10.9	13.5	12.6
12	5.7	6.0	5.2
14	5.3	5.4	4.6
16	4.9	5.1	4.3
17	4.4	4.6	3.8
19.5	3.8	4.0	3.2

Drying curves for five batches produced by this route are shown in FIG. 2.

$La_2(CO_3)_3.3.8H_2O$ from dish 1 was selected as Sample 6 for the phosphate binding tests set forth in Table 1.

EXAMPLE 2

The process of Example 1 was repeated but using hydrochloric acid (12.28M, 2.48 litres) in place of nitric acid to dissolve lanthanum oxide (1.5 kg). The yield of crude product after six washes was 4.378 kg. The product was divided in three approximately equal portions in Pyrex dishes and dried in a fan oven at 80° C. After 2 hours a sample was taken from each tray and water analysed by decomposition to lanthanum oxide as described above. These figures were used to calculate the weight loss needed to give material of the required composition. The time course of the drying process is shown below.

Time	mol H_2O/La		
(hours)	Dish 1	Dish 2	Dish 3
2	21.3	22.1	20.4
5.5	12.3	13.2	12.2
9	7.9	8.0	7.6
11.5	6.9	7.0	6.6
17	4.9	5.1	4.6
18.5	4.6	4.8	4.2
19.5	4.4	4.6	4.1
20	4.3	4.6	4.0

Samples were taken from each dish, combined and analysed. The following results were obtained:

	Found	Calculation for $La_2(CO_3)_3.4H_2O$
% La (gravimetric)	52.38%	52.4%
carbonate (titration)	5.76 mol/g	5.66 mol/g
H_2O (NMR)	13.06%	13.59%

The XRD analysis for lanthanum carbonate $4H_2O$ prepared by the method of Example 2 is illustrated in FIG. 3.

FIG. 4 illustrates the XRD of lanthanum carbonate $8.8H_2O$ and it is evident that it has a different crystalline structure from lanthanum carbonate $4H_2O$ prepared by the method of Example 2. The XRD analysis of lanthanum carbonate $4H_2O$ prepared by the method of Example 1 was similar to the XRD analysis of lanthanum carbonate $4H_2O$ prepared by the method of Example 2.

Pharmaceutical compositions for oral administration according to the invention may be formulated and manufactured using methods well known in the art. Suitable diluents or carriers are also well known. The compositions may desirably be in a dosage form, to provide a single daily dose, or a number of sub-daily dosages. Conventional pharmacological methods may be used to ascertain suitable dose levels. The level of phosphate in the food that an individual ingests is important. Daily dosages are indicated to be in the range 0.1 to 50 g, preferably about 0.5 to 15 g. Suitable forms for oral administration include solid forms such as tablets, capsules and dragees and liquid forms such as suspensions or syrups. In addition to diluents and carriers, it is conventional in the formulation of oral preparations to include non-active ingredients such as thickeners, taste-improving components and colouring agents. The said carbonate may also be coated or treated to provide delayed-release forms. Preferably, the required daily dosage is given in tablet form, eg chewable tablet form, to be taken with meals. A suitable daily dosage of about 2 g for 70 kg man, should be compared with a daily dosage of 20 g for a commercial calcium-based phosphate binding composition.

To demonstrate that the lanthanum carbonate of the invention (or lanthanum phosphate formed after binding to phosphate in the gut) is fully excreted and does not pass out of the gut into the circulation system when given orally, three rats were dosed with 20 mg/kg of $La_2(CO_3)_3.4H_2O$ (Sample 5) and kept in metabolic cages where faeces and urine could be collected. The results are shown in Table 2 below.

Animal No.	Time (hours)	% La Recovered
1	24	103.2
1	48	0.1
1	72	<0.2
1	Total	103.3
2	24	75.3
2	48	23
2	72	1.2
2	Total	99.5
3	24	93.8
3	48	10
3	72	0.1
3	Total	103.8

It can be seen that after 72 hours, all of the lanthanum has been excreted. In the urine samples, the amount of lanthanum was below detection limits. After the test, the rats were sacrificed, and kidney, liver and femur were analysed for lanthanum. In all cases, the amount of lanthanum was below 0.1 ppm.

We claim:

1. A pharmaceutical composition for the treatment of hyperphosphataemia comprising lanthanum carbonate of the formula

$$La_2(CO_3)_3.xH_2O$$

where x has a value from 3 to 6, in admixture with a pharmaceutically acceptable diluent or carrier in a form for administration to the gastrointestinal tract.

2. A composition according to claim 1, wherein x has a value from 3.5 to 5.

3. A composition according to claim 2, wherein x has a value from 3.8 to 4.5.

4. A composition according to any one of claims 1 to 3 in unit dosage form to provide from 0.1 to 20 g/day.

5. A process for the preparation of lanthanum carbonate as defined in any one of claims 1 to 3 which comprises the steps of:

(i) reacting lanthanum oxide with hydrochloric acid to obtain lanthanum chloride;

(ii) reacting a solution of the thus obtained lanthanum chloride with an alkali metal carbonate to produce a wet cake of lanthanum carbonate octahydrate; and

(iii) drying the wet cake of lanthanum carbonate octahydrate so as to obtain a lanthanum carbonate with 3 to 6 molecules of water of crystallisation.

6. A process as claimed in claim 5 wherein the alkali metal carbonate is sodium carbonate.

7. A method to treat hyperphosphataemia in a subject which method comprises administering to said subject an amount of lanthanum carbonate of the formula

$$La_2(CO_3)_3.xH_2O$$

wherein x has a value from 3 to 6 effective to treat said hyperphosphataemia.

8. The method of claim 7 wherein x has a value from 3.5 to 5.

9. The method of claim 8 wherein x has a value from 3.8 to 4.5.

10. The method of any of claims 7–9 wherein said administering is by an oral route.

* * * * *

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Close Date	10/20/2003	10/19/2007	10/19/2011

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NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA

Submission No.	Type of Submission	To/From	Date
095	General Correspondence: Final Draft Labels and Labeling	To: Dr. Stockbridge Fm: L. Wittmer	10/20/04
094	General Correspondence: Request for Type C Meeting	To: Dr. Stockbridge Fm: L. Wittmer	10/21/04
Regcon	To discuss timings and plan for submission of launch materials to DDMAC	To: L. McLeroy & M. Kiester Fm: D. Ahern	10/19/04
Regcon	To discuss the status of the Agency's feedback on the optimized formulation, and to confirm the upcoming Nov. 16 FDA meeting	To: D. Hinton Fm: L. Wittmer	10/18/04
093	General Correspondence: Final Draft Labeling (revised)	To: EDR Fm: D. Ahern	10/14/04
Email	Fosrenol labeling: final draft labeling with deletions as agreed by FDA, and corrected misspelled word of "administered"	To: D. Hinton Fm: L. Wittmer	10/12/04
092	General Correspondence: Final Draft Labeling	To: EDR Fm: D. Ahern	10/11/04
Email	Bottle label revisions	To: D. Hinton Fm: L. Wittmer	10/8/04
Email	Revised sample bottle label (250mg) for patient sample to match commercial labels	To: D. Hinton Fm: L. Wittmer	10/8/04
Email	Fosrenol labeling: supportive data packet for reference	To: D. Hinton Fm: L. Wittmer	10/6/04
Email	Fosrenol labeling: updated PI to reflect FDA's comments; alternative presentation of the AE section	To: D. Hinton Fm: L. Wittmer	10/6/04

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
091	CMC Amendment: Withdrawal of optimized formula, 250, 500, 750, and 1000mg.	To: Dr. Stockbridge Fm: L. Wittmer	10/1/04
Email	Updated PI with tentative agreements made with the Agency	To: D. Hinton Fm: L. Wittmer	10/1/04
Email	Feedback on FDA's proposed wording for PI	To: Dr. Stockbridge Fm: L. Wittmer	9/20/04
Email	Additional revision to Fosrenol PI (change to line 64)	To: D. Hinton Fm: L. Wittmer	9/15/04
Email	Proposed package insert for Fosrenol in Word, and side-by-side comparison of the wording (FDA vs. Shire)	To: Dr. Raman Fm: L. Wittmer	9/13/04
090	General Correspondence: CMC (commitment to place first 3 validation/production batches on stability per SN086)	To: Dr. Stockbridge Fm: L. Wittmer	9/10/04
Email	Additional information wrt the proposed commercial pack (500mg/100count)	To: Dr. Raman Fm: L. Wittmer	9/10/04
Email	Information on double-blind studies for PI	To: D. Hinton Fm: L. Wittmer	9/7/04
089	CMC Amendment: Updated lanthanum carbonate specification and test methods for 250mg and 500mg current formula to support the use of Apparatus 2 dissolution method	To: Dr. Stockbridge Fm: L. Wittmer	9/2/04
088	General Correspondence: Meeting Minutes (CMC and Biopharm Teleconference 27-Aug-04)	To: Dr. Stockbridge Fm: L. Wittmer	9/2/04

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
087	General Correspondence: Pharmacovigilence Risk Management Plan Supplement	To: Dr. Stockbridge and Desk Copy Hinton Fm: L. Wittmer	9/1/04
Regcon	To discuss an email sent to FDA on 8/19/04 regarding Biopharm and CMC issues	To: D. Hinton Fm: L. Wittmer	8/26/04
Regcon	Discuss Fosrenol Pharmacovigilance Risk Management Plan with FDA	To: D. Hinton and FDA Fm: D. Ahern and Team	8/19/04
086	Response to Request for Information – CMC Section (Cumulative Revisions)	To: Dr. Stockbridge and FIELD OFFICE COPY Fm: L. Wittmer	8/18/04
085	Response for Request for Information – Revised Labels and Labeling	To: FDA Central Document Room/EDR Fm: L. Wittmer	8/11/04
084	General Correspondence: CMC Correction to Zirconium specification	To: Dr. Stockbridge Fm: L. Wittmer	8/06/04
Letter	Desk copies of ISE Submission No. 000 Volume 1.78, ISE 15-month submission No. 066 (Volumes 17-36) and ISS 25-month No. 074 (Volumes 1-3)	To: D. Hinton Fm: L. Wittmer	7/29/04
083	Response to Request for Information (Updated current formulation specs)	To: Dr. Stockbridge Fm: L. Wittmer	7/26/04
082	Response to Request for Information (Dissolution data and update specifications; Pharmacodynamic equivalence – responses to inspection items; Sample bottle labels)	To: Dr. Stockbridge Fm: L. Wittmer	7/23/04
Email	Response to request for AEs treatment emergent by age group	To: D. Hinton Fm: L. Wittmer	7/22/04
Email	Error on pack size of 250cc instead of 300cc; will forward new artwork with correct dimensions	To: D. Hinton Fm: L. Wittmer	7/22/04
Email	Confirmed that USP names of inactives should be used for bottle labels	To: Dr. Raman Fm: L. Wittmer	7/21/04
Email	Current formulation bottle labels	To: D. Hinton Fm: L. Wittmer	7/21/04

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
Email (regcon)	FDA agreed with API specs proposal	To: Dr. Raman Fm: J. Ferdinando	7/19/04
Email	Response to clinical questions (safety and efficacy analyses on subpopulation of patients over 65 years old; fracture analysis for 25-month ISS dataset)	To: D. Hinton Fm: L. Wittmer	7/19/04
Regcon	To let Denise know to expect one bottle each of 250 mg and 500 mg tablets	To: D. Hinton Fm: K. Epperly	7/19/04
Letter	Samples of 250 mg and 500 mg tablets	To: D. Hinton Fm: L. Wittmer	7/19/04
Email	More info on 250 mg current formulation dissolution testing using Apparatus 2	To: Dr. Raman Fm: J. Ferdinando	7/19/04
Email	Updated lanthanum oxide specification	To: Dr. Raman Fm: J. Ferdinando	7/19/04
Email	SPD405-116 Inspections (Shire's response to the 483s issues to vendors) updated scanned copies	To: D. Hinton Fm: L. Wittmer	7/16/04
Email	Crushed tablet dissolution data	To: Dr. Raman Fm: J. Ferdinando	7/15/04
Email	Raw data for the other dissolution media to the data provided to Dr. Dorrantes	To: D. Hinton Fm: L. Wittmer	7/15/04
Email	SPD405-116 Inspections (Shire's response to the 483s issues to vendors)	To: D. Hinton Fm: L. Wittmer	7/14/04
Email	Expanded dissolution data as requested on the current formulation	To: Dr. Raman Fm: J. Ferdinando	7/14/04
Email	Fracture rates (updated tables to respond to Dr. Williams' concerns that the fracture rates by exposure category may be misleading due to patients with minimal lanthanum exposure were included in the analysis)	To: Dr. Williams Fm: L. Wittmer	7/13/04
Email	Current formulation dissolution profiles (individual profiles for 250mg and 500mg tablets)	To: D. Hinton Fm: L. Wittmer	7/13/04

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
081	Uremic Rat Bone - Pathology report	To: Dr. Stockbridge Fm: L. Wittmer	7/12/04
080	CMC Amendment (Updated metal specification, including scandium and indium; Updated hardness specifications; Commitment that blend uniformity will be an in-process test; Lanthanum hydroxycarbonate LOQs)	To: Dr. Stockbridge Fm: L. Wittmer	7/12/04
Regcon	To reconcile FDA's requests for information with what has been submitted; To request feedback on biopharm review, specifically feedback on the inspection results; To request update from FDA's internal labeling meeting; To confirm scheduled labeling discussion on 7/15/04	To: D. Hinton Fm: L. Wittmer	7/9/04
Email	Updated tablet spec which include the tightened hardness limits	To: Dr. Raman Fm: J. Ferdinando	7/9/04
Email	Statement from Shire committing to test scandium and indium with safety justifications for the limits; authorized revised specs to reflect new levels of metals in the API	To: Dr. Raman Fm: J. Ferdinando	7/9/04
Email	GI and MS AE event tables	To: D. Hinton Fm: L. Wittmer	7/9/04
079	CMC Amendment (Dissolution Data Update and Biowaiver Report)	To: Dr. Stockbridge Fm: L. Wittmer	7/8/04
Email	Fracture tables adjusted for discontinuations	To: D. Hinton Fm: L. Wittmer	7/8/04
Email	Confirmation regarding adding Indium and Scandium to API specs	To: Dr. Raman Fm: J. Ferdinando	7/8/04
Email	Blend uniformity; chewability and hardness; metal impurity testing of API; XRD method	To: Dr. Raman Fm: J. Ferdinando	7/7/04
078	Table outlining studies in which healthy volunteer have received lanthanum	To: Dr. Stockbridge Fm: L. Wittmer	7/6/04
Email	Clarification on LOQ values and specifications for tablets	To: D. Hinton Fm: J. Ferdinando	7/2/04

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
Regcon	Telecon to discuss ongoing CMC issues	To: Dr. Raman Fm: Jo Ferdinanco	6/29/04
Email	Proposed Packaging Configurations	To: D. Hinton Fm: R. Lilley	6/25/04
Email	Response to CMC Review Questions from 17-Jun-04 meeting	To: Dr. Raman Fm: R. Lilley	6/25/04
077	General Correspondence: Response to FDA Request for Information (summary of fracture data)	To: Dr. Stockbridge Fm: L. Wittmer	6/24/04
076	General Correspondence: Meeting Summary from 17-Jun-2004 (with attachments on GI AE outcomes adjusted, clarification of mortality analysis, reviewer's guide to GI AE data, and guide to bone fracture data)	To: Dr. Stockbridge Fm: L. Wittmer	6/21/04
Email	Line-numbered annotated labeling (Word and PDF versions)	To: D. Hinton Fm: L. Wittmer	6/21/04
Email	Response to Dr. Williams' request for info on number of patients with diabetes in studies, and patients who had bone biopsies	To: D. Hinton Fm: L. Wittmer	6/15/04
Email	Bone histology	To: Dr. Williams Fm: L. Wittmer	6/11/04
075	Briefing Package for FDA Meeting on 11-Jun-2004	To: Dr. Stockbridge Fm: L. Wittmer	6/2/04
074	General Correspondence: Request for Information (Safety Update for LAM-IV-307)	To: Dr. Stockbridge Fm: L. Wittmer	6/1/04
073	CMC Amendment (Dissolution Method Devt, Updated Stability Reports for API, Optimized Formulation and Current Formulation)	To: Dr. Stockbridge Fm: L. Wittmer	5/28/04
Email	Overview of Risk Management Plan	To: D. Hinton Fm: L. Wittmer	5/24/04

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
Regcon	To request an update from FDA's internal review meeting	To: D. Hinton Fm: L. Wittmer	5/18/04
Email	Request clarification regarding Dr. Williams' statement referring to slides/study of bone histology data	To: Dr. Williams Fm: L. Wittmer	5/6/04
071	General Correspondence: Bioanalytical Reports for the plasma/urine lanthanum assays	To: Dr. Throckmorton Fm: L. Wittmer	5/6/04
072	General Correspondence: Response to Information Request Letter (bone histological slides)	To: Dr. Throckmorton Fm: L. Wittmer	5/5/04
Email	Copy of Shire's internal tracking of correspondence/submission to FDA	To: D. Hinton Fm: L. Wittmer	4/20/04
Email	Follow-up on request for bone biopsy reference	To: D. Hinton Fm: L. Wittmer	4/14/04
Email	Propose an incremental safety update (ISS)	To: Dr. Throckmorton Fm: L. Wittmer	4/14/04
Email	Follow-up on proposal to provide 18-mos stability data on Boots tablet batches at the end of May	To: Dr. Raman Fm: L. Wittmer	4/13/04
Email	Follow-up on 1) FDA request for survival data for patients excluded from lanthanum carbonate clinical studies; 2) feedback on justification for examining bone toxicities using histomorphometry (SN068); 3) adequacy of PD equivalence data	To: Dr. Throckmorton Fm: L. Wittmer	4/8/04
070	Response to Request for Information (CMC)	To: Dr. Throckmorton Fm: L. Wittmer	4/1/04
069	Response to Request for Information (Gastrointestinal AE)	To: Dr. Throckmorton Fm: L. Wittmer	4/1/04
Regcon	- To discuss the timeframe for submission of the stability and safety updates; and - To discuss the timing of receipt of the request for information letter	To: D. Hinton Fm: L. Wittmer	3/29/04
Email	Outlines Shire's actions resulting from our recent telephone conference with the Biopharmaceutics and Chemistry reviewers on 10 March 2004	To: D. Hinton Fm: L. Wittmer	3/23/04

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
068	Response to FDA Request for Information (rationale for histomorphometric interpretation of bone biopsy data; fracture analysis; mortality data)	To: Dr. Throckmorton Fm: L. Wittmer	3/22/04
Email	Follow-up re: Dr. Williams' comment about patient profiles not readable	To: D. Hinton Fm: L. Wittmer	3/16/04
Email	Clinical mass balance study	To: D. Hinton Fm: L. Wittmer	3/16/04
Email	To provide response timings of FDA request for info from the resubmission filing, and to request a letter from the Division in order to address specific questions raised	To: D. Hinton Fm: L. Wittmer	3/11/04
Email	Preliminary response to Dr. Dorantes' question regarding fecal excretion data from orally-dosed subjects	To: D. Hinton Fm: L. Wittmer	3/8/04
Email	Will respond to request for number of patients in each group with at least one GI event with duration >28 days/unresolved	To: V. Freidlin Fm: L. Wittmer	3/5/04
Email	Table 1 of resolution of GI AE, source tables and SAS program	To: D. Hinton Fm: L. Wittmer	3/3/04
Email	Mortality analyses update (for discussion during teleconference with FDA on 3/2/04)	To: D. Hinton Fm: L. Wittmer	3/1/04
Email	Table 2 of proposed package insert with incidence of AE adjusted for exposure	To: D. Hinton Fm: L. Wittmer	3/1/04
Email	General inquiry regarding review time and feedback on bioequivalence data for study SPD405-116	To: D. Hinton Fm: L. Wittmer	2/23/04
Email	Provide official address of additional analytical testing lab (RSSL), as requested	To: Dr. Raman Fm: L. Wittmer	2/17/04
Email	Additional documents that were not included in the resubmission: - LAM-IV-307 (2nd interim report) - Patient listings - LAM-IV-301e (report addendum) - Case report forms for SAEs and	To: D. Hinton Fm: L. Wittmer	2/4/04

	study discontinuations		

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
067	Resubmission of Electronic Component of New Drug Application	To: Dr. Throckmorton Fm: L. Wittmer	2/2/04
066	Resubmission of New Drug Application (89 volumes on shelf)	To: Dr. Throckmorton Fm: L. Wittmer	1/26/04
Regcon	1) Ask questions regarding the format and content of the resubmission, 2) Confirm receipt of protocol 312 and the accompanying CMC amendment, and 3) Request feedback on bioequivalence.	To: D. Hinton Fm: L. Wittmer	1/14/04
Email	Follow-up items from 3-Dec-2003 FDA meeting	To: D. Hinton Fm: L. Wittmer	12/9/03
Email	Updated list of Shire attendees for FDA meeting on 3-Dec-2003	To: D. Hinton Fm: G. Miller	12/2/03
Regcon	To request a meeting confirmation and preliminary feedback from FDA regarding the briefing package for the 3 December 2003 meeting.	To: D. Hinton Fm: L. Wittmer	11/25/03
065	Clinical Amendment: Final Clinical Study Report SPD405-116	To: Dr. Throckmorton Fm: L. Wittmer	11/25/03
064	Pre-resubmission Briefing Package (to be held on 3-Dec-2003)	To: Dr. Throckmorton Fm: L. Wittmer	11/10/03
Email	Additional bone lanthanum and histomorphometry data that will be included in the briefing package for the upcoming 3 December 2003 meeting.	To: D. Hinton Fm: L. Wittmer	10/28/03
Email	Additional information on the SPD405-116 study to fulfil FDA's request for retrospective power estimation for the 116 study (per the teleconference on 21 October 2003).	To: D. Hinton Fm: L. Wittmer	10/28/03
Regcon	To provide the preliminary results of the analysis of additional biopsies (bone lanthanum levels) to FDA so that they are prepared to receive the briefing package next week and able to give us some feedback of impact on ongoing activities, particularly the 3b program.	To: D. Hinton Fm: L. Wittmer	10/27/03

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
Email	Bioequivalence (Optimized Formulation) PK Data Preliminary PK data from 116 study	To: D. Hinton Fm: L. Wittmer	10/15/03
Regcon	Inquire about the acceptability of urinary phosphate in healthy volunteers as a measure of bioequivalence (FDA feedback on submission #062).	To: D. Hinton Fm: L. Wittmer	10/15/03
063	General Correspondence: Copy of USAN Letter	To: Dr. Throckmorton Fm: L. Wittmer	9/5/03
062	General Correspondence: BE Study Justification	To: Dr. Throckmorton Fm: L. Wittmer	8/27/03
061	General Correspondence: Meeting summary from 7-Aug-03 FDA meeting	To: Dr. Throckmorton Fm: L. Wittmer	8/27/03
060	Meeting Information Package (Revision)	To: Dr. Throckmorton Fm: L. Wittmer	8/4/03
Email	Additional dissolution figure (for meeting info package)	To: D. Hinton Fm: L. Wittmer	8/4/03
059	Meeting Information Package (CMC meeting on 7-Aug-03)	To: Dr. Throckmorton Fm: L. Wittmer	7/21/03
Email	To inform CSO the CMC briefing packet will be hand-delivered tomorrow morning.	To: D. Hinton Fm: L. Wittmer	7/21/03
058	General Correspondence: Meeting summary from 3-Jul-03 FDA meeting	To: Dr. Throckmorton Fm: L. Wittmer	7/14/03
057	General Correspondence: Meeting summary from 26-Jun-03 CMC teleconference	To: Dr. Throckmorton Fm: L. Wittmer	7/14/03
Email	Bioequivalence question – 500 mg and optimized formulations of lanthanum carbonate	To: D. Hinton Fm: L. Wittmer	7/1/03
Regcon	FDA CMC teleconference meeting regarding stability requirements for optimized formulation	To: Denise Hinton, Patrick Marroum, Angelica Dorrantes, Chris Raman, Dr. Srinivasachar Fm: L. Wittmer & Jo Ferdinando	6/26/03

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
Email	Optimized formulation (lanthanum carbonate) – stability question (background information for discussion on 26-Jun-03 with Drs. Raman and Srinivasachar)	To: D. Hinton Fm: L. Wittmer	6/25/03
056	General Correspondence: Request for Type C Meeting	To: Dr. Throckmorton Fm: L. Wittmer	6/25/03
Email	Draft CMC Meeting Request	To: D. Hinton Fm: L. Wittmer	6/18/03
Email	Optimized formulation (lanthanum carbonate) – stability question	To: D. Hinton Fm: L. Wittmer	6/18/03
Email	Open issues re: 1) API water spec agreement, 2) feedback on 3b study synopsis and 3) feedback on biostudy (SPD405-116)	To: D. Hinton Fm: L. Wittmer	5/23/03
Regcon	Inquire about the process and timing of responding to the action letter.	To: D. Hinton Fm: L. Wittmer	5/12/03
Email	Questions on optimized formulation of Fosrenol	To: D. Hinton Fm: L. Wittmer	5/6/03
055	General Correspondence – CMC (Response to FDA Questions: Factorization agreement)	To: Dr. Throckmorton Fm: L. Wittmer	5/2/03
054	General Correspondence – Request for Feedback on BE Study Synopsis (SPD405-116)	To: Dr. Throckmorton Fm: L. Wittmer	5/2/03
053	General Correspondence – CMC (Response to FDA Questions on factorization issue - revised)	To: Dr. Throckmorton Fm: L. Wittmer	4/24/03
Regcon	Inquire about the Agency's response to our question regarding the use of factorization in the manufacture of lanthanum carbonate.	To: Denise Hinton Fm: L. Wittmer	4/22/03
052	General Correspondence – CMC (Response to FDA Questions on factorization issue)	To: Dr. Throckmorton Fm: L. Wittmer	4/11/03
051	General Correspondence – Meeting Summary (27 March 03)	To: Dr. Throckmorton Fm: L. Wittmer	4/10/03

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
Regcon	• To discuss whether Shire may use factorization in the manufacture of production batches of lanthanum carbonate. • To request feedback on our proposal to apply for a bio-waiver for the 500 mg tablet • To discuss whether a disintegration method could be use during long-term QC analysis of drug product batches	To: Denise Hinton, Kris Raman (CMC Reviewer), Kasturi Srinivasachar (CMC Reviewer) and Patrick Marroum (Biopharmaceutics Reviewer) Fm: Lisa Wittmer and Jo Ferdinando	4/2/03
Regcon	1) To confirm CMC teleconference scheduled for 2 April 2003 to discuss factorization. 2) To request a teleconference with Dr. Dorantes (Clin Pharm & Biopharmaceutics) and at least one of the Pharmacology reviewers to discuss bio-waiver/bio-study options for supporting approval of the 500 mg tablet.	To: Denise Hinton Fm: L. Wittmer	3/31/03
050	General Correspondence – CMC Response to FDA Questions (analytical method and validation reports in response to 1/16/03 FDA letter)	To: Dr. Throckmorton Fm: L. Wittmer	3/31/03
Regcon	1) To request that the CMC reviewers provide an answer to Shire's question regarding the use of factorisation to achieve a fully potent product, and request a teleconference, if necessary. 2) To discuss follow-up items from the March 27th meeting.	To: Denise Hinton Fm: L. Wittmer	3/28/03
049	General Correspondence - Pre Meeting Briefing Documents (hard copies of slides)	To: Dr. Throckmorton Fm: Mark McLoudrey	3/24/03
Email	To clarify a question for Chemistry reviewer with regard to factorization issue	To: Denise Hinton Fm: M. McLoudrey	3/24/03
048	General Correspondence - Notice of Intent to File an Amendment and Request for Teleconference in Response to FDA Approvable Action Letter Dated	To: Dr. Throckmorton Fm: Mark McLoudrey	3/07/03

	02/28/03		

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
Email	To seek clarification on approvable letter dated 28-Feb-03	To: Denise Hinton Fm: M. McLoudrey	3/3/03
Email	FDA's request for Word version of ISE/ISS (from original NDA submission file)	To: Denise Hinton Fm: M. McLoudrey	2/21/03
Email	Call-in information for conference call on 21-Feb-03	To: Denise Hinton Fm: M. McLoudrey	2/20/03
047	General Correspondence – Response to Statistical Reviewer's Request for Information (fracture-related AEs)	To: Dr. Throckmorton Fm: G. Miller	2/12/03
Email	Response to Statistical Reviewer's Request for Information (via email on 2/11/03) (note: this set is comprised of 6 related email messages – 2/11/03-2/13/03).	To: Dr. Freidlin Fm: G. Miller	2/12/03
Regcon	To inquire the status of teleconference to discuss the contents of the action letter for the NDA.	To: Denise Hinton Fm: G. Miller	2/12/03
Regcon	Request for early issuance of action letter	To: Denise Hinton Fm: M. McLoudrey	1/28/03
Email	Further clarification on Subm 045 (response to statistical reviewer's request) sent via email by Dr. Freidlin on 1/28/03 @ 10:06am	To: Dr. Freidlin Fm: G. Miller	1/28/03
046	General Correspondence: Response to CMC Information Request (reference to conversation on 1/15/03 between Ms. Hinton and Dr. Wittmer)	To: Dr. Throckmorton Fm: L. Wittmer	1/28/03

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
045	General Correspondence: Response to Statistical Reviewer's Request (clarification of data representing death rate; CD-ROM incl.)	To: Dr. Throckmorton Fm: L. Wittmer	1/27/03
044	General Correspondence: Response to Medical Reviewer's Request (summary of cause of death based on latest available retrospective analysis of mortality)	To: Dr. Throckmorton Fm: L. Wittmer	1/23/03
Regcon	1) To get an update regarding topics that were discussed during the internal FDA meeting on Monday, January 6, 2003 to discuss the review of the NDA. 2) Had Fosrenol™ been approved as the brand name for lanthanum carbonate?	To: Denise Hinton Fm: L. Wittmer	1/7/03
Regcon	To get an update on the NDA review for Fosrenol	To: Denise Hinton Fm: L. Wittmer	1/2/03
Email	Bone fracture data by study	To: Dr. Pelayo Fm: L. Wittmer	12/24/02
043	General Correspondence: Response to Statistical Reviewer's and Medical Reviewer's Requests (changes in QTc, SAS programs, clarifications on ECG analysis report, summary of ECG data in Phase 2-3)	To: Dr. Throckmorton Fm: L. Wittmer	12/23/02
Email	ECG data available from Phase 2-3 studies	To: Dr. Pelayo Fm: L. Wittmer	12/23/02

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
042	General Correspondence – Clinical Information (mortality analysis, AE profile and bone fracture analysis)	To: Dr. Throckmorton Fm: L. Wittmer	12/20/02
041	General Correspondence – Response to CMC Reviewer's Request for Information	To: Dr. Throckmorton Fm: L. Wittmer	12/20/02
Email	NDA 21-468, Study 307, Visit 21, No. of patients (ECG Tables for 205, 204, 302)	To: Dr. Freidlin Fm: L. Wittmer	12/19/02
040	General Correspondence – Meeting Minutes (from the CMC teleconference held on December 12, 2002 to discuss the review of the NDA for lanthanum carbonate hydrate)	To: Dr. Throckmorton Fm: L. Wittmer	12/18/02
Email	NDA 21-468, Study 307, Visit 21, No. of patients (Response to statistical reviewer's request for ECG analysis report, table 2 for 307)	To: Dr. Freidlin Fm: L. Wittmer	12/18/02
Email	NDA 21-468, Study 307, Visit 21, No. of patients (QTc data from study 308)	To: Dr. Freidlin Fm: L. Wittmer	12/17/02
Email	Meeting Minutes for CMC meeting (held on 12 Dec 2002)	To: Denise Hinton Fm: L. Wittmer	12/16/02
039	General Correspondence – Response to Statistical Reviewer's Request	To: Dr. Throckmorton Fm: L. Wittmer	12/16/02
038	Amendment – Chemistry Manufacturing and Controls (packaging of lanthanum carbonate chewable tablets)	To: Dr. Throckmorton Fm: L. Wittmer	12/13/02
037	Electronic Submission - Fosrenol Bottle Labels for the 250 and 500 mg tablets	To: Dr. Throckmorton Fm: L. Wittmer	12/13/02
Email	Update to Table 2 of ECG Analysis Report of Protocol LAM-IV-307 (using 4-month safety database)	To: Dr. Freidlin Fm: L. Wittmer	12/13/02
Email	Bottle labels	To: Denise Hinton Fm: L. Wittmer	12/09/02
036	General Correspondence-Meeting Minutes from Dec 3	To: Dr. Throckmorton Fm: L. Wittmer	12/06/02

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
Email	Deficiency list	To: Denise Hinton Fm: L. Wittmer	12/06/02
Regcon	To ask for clarification on the findings of the CAC review for Fosrenol	To: Denise Hinton Fm: L. Wittmer	12/04/02
Email	Clarification of calculation of patients exposed in Phase 2/3 studies (4 month safety update)	To: Denise Hinton Fm: L. Wittmer	12/03/02
Email	SAS program for calculating QTc changes	To: Dr. Freidlin Fm: L. Wittmer	12/03/02
035	General Correspondence – CMC Information (dissolution method redevelopment report)	To: Dr. Throckmorton Fm: L. Wittmer	11/27/02
034	Electronic File (Proposed package insert)	To: Central Doc Room Fm: L. Wittmer	11/27/02
033	General Correspondence – CMC Information (stability data to support shelf-life)	To: Dr. Throckmorton Fm: L. Wittmer	11/27/02
Email	General Correspondence – CMC Information (stability data to support shelf-life)	To: Denise Hinton Fm: L. Wittmer	11/27/02
Regcon	To confirm that a separate IND was not required for studies conducted with the optimized formulation (same dose form)	To: Denise Hinton Fm: L. Wittmer	11/27/02
Email	Package insert for Fosrenol (Word file)	To: Denise Hinton Fm: L. Wittmer	11/27/02
Email	Package insert for Fosrenol (pdf file)	To: Dr. Freidlin Fm: L. Wittmer	11/22/02
032	Electronic File (with paper copy) – SAS Program used to calculate phosphate levels in LAM-IV-307	To: Central Doc Room Fm: L. Wittmer	11/22/02
031	Electronic File (with paper copy) – ECG datasets for studies 204, 205, 302 and 308 - ECG dataset for study 307 with changes as requested by Biostat reviewer - Results of ECG for 307	To: Central Doc Room Fm: L. Wittmer	11/22/02

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
030	General Correspondence – Clinical Information (up-to-date mortality analyses)	To: Dr. Throckmorton Fm: L. Wittmer	11/21/02
029	Electronic File (Response to FDA Request for Additional Clinical Data for Changes from Baseline in Phosphate Levels and p-Values)	To: Central Document Room Fm: L. Wittmer	11/15/02
028	Electronic File (Response to FDA Request for ECG Dataset of Study 307)	To: Central Document Room Fm: R. Lilley	11/11/02
RegCon	To follow-up on the internal agency meeting	To: Denise Hinton Fm: S. Krishnan	11/05/02
027	General Correspondence – Additional CMC Information and response to questions raised at 90-day meeting	To: Dr. Throckmorton Fm: R. Lilley	11/04/02
026	General Correspondence – Response to FDA Request (assessment of potential interaction with concomitant meds)	To: Dr. Throckmorton Fm: R. Lilley	11/01/02
025	General Correspondence – Response to Preclinical Questions at teleconference on 10/23/02 with Dr. Joseph	To: Dr. Throckmorton Fm: R. Lilley	10/28/02

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
024	General Correspondence – Response to Preclinical Request (Tumor data for CD-1 mouse)	To: Dr. Throckmorton Fm: R. Lilley	10/24/02
RegCon	Teleconference with Dr. Joseph to discuss progress of the preclinical review	To: Dr. Xavier Joseph Fm: Suma Krishnan, Steve Damment, Isobel Webster, Mike Burkin	10/23/02
023	General Correspondence – Response to FDA Question (Discrepancy in the no. of liver tumours in male rats)	To: Dr. Throckmorton Fm: R. Lilley	10/22/02
022	General Correspondence – Response to FDA Request (Time to event analysis related to fractures)	To: Dr. Throckmorton Fm: S. Krishnan	10/08/02
RegCon	To request for a teleconference to discuss gene toxicity concerns.	To: Dr. Xavier Joseph Fm: S. Krishnan	10/04/02
RegCon	To inform the Agency on the status of their requested information for time to event analysis on GI and AEs	To: Dr. Valeria Friedman Fm: S. Krishnan	10/04/02
021	General Correspondence – Response to FDA Request (Statistical time to event analysis)	To: Dr. Throckmorton Fm: S. Krishnan	10/03/02
020	General Correspondence – Response to FDA Request (Nonclinical Pharm and Tox on missing page in SPD /88/C)	To: Dr. Throckmorton Fm: S. Krishnan	09/25/02
019	General Correspondence – CMC Copy of DMF authorization letter)	To: Dr. Throckmorton Fm: S. Krishnan	09/18/02
018	General Correspondence – Response to FDA Request (CMC request for DMF#)	To: Dr. Throckmorton Fm: S. Krishnan	09/16/02
017	General Correspondence – Ninety Day Meeting Minutes from 9/5/02 meeting	To: Dr. Throckmorton Fm: S. Krishnan	09/13/02
016	**Resubmission of Electronic Files** for Four Month Safety Update – Integrated Summary of Safety	To: CDR Fm: S. Krishnan	09/10/02
015	General Correspondence – Response to FDA Request (NonClinical Pharmacology and Toxicology for statistical analysis report on carcino studies)	To: Dr. Throckmorton Fm: S. Krishnan	08/30/02

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
014	Electronic Files for Four Month Safety Update – Integrated Summary of Safety	To: Dr. Throckmorton Fm: S. Krishnan	08/30/02
013	Four Month Safety Update – Integrated Summary of Safety (32 acco volumes on shelf)	To: Dr. Throckmorton Fm: S. Krishnan	08/30/02
012	General Correspondence – CMC on updated specs and test method for drug substance and tablets	To: Dr. Throckmorton Fm: S. Krishnan	08/29/02
Letter	General Correspondence – Change of Address (note to file: audit 4/16/2003-letter is unsigned & plain bond)	To: Dr. Throckmorton Fm: S. Krishnan	08/29/02
011	General Correspondence – Briefing Package (Ninety Day Meeting on 9/5/02)	To: Dr. Throckmorton Fm: S. Krishnan	08/27/02
010	General Correspondence – Response to FDA request (Biopharmaceutics on dissolution method justification)	To: Dr. Throckmorton Fm: S. Krishnan	08/27/02
RegCon	Enquire about the status of the NDA review	To: D. Henton Fm: S. Krishnan	08/23/02
009	General Correspondence – Response to FDA Request (Nonclinical Pharmacology and Toxicology for rationale and justification for excluding beryllium from list of specified metal contaminants, and selection of maximum tolerated dose for long term carcino studies)	To: Dr. Throckmorton Fm: S. Krishnan	08/14/02
008	**Resubmission of Electronic Files** for Study Reports 202, 204, 301, 302, 307 and Carcinogenicity Studies	To: Electronic Doc. Rm Fm: S. Krishnan	08/05/02
007	General Correspondence-Response to FDA Request for Additional Information (list of countries that Calcium Carbonate was approved for treatment of hyperphosphatemia)	To: Dr. Throckmorton Fm: S. Krishnan	07/30/02
Desk Copy	Request for 2 additional copy of Investigator's Brochure	To: D. Henton Fm: S. Krishnan	07/25/02
Electronic Files	Electronic copies of Study Reports, Protocols, and Statistical Plans for 202, 204, 301, 302, 307, and	To: Electronic Document Room Fm: S. Krishnan	07/25/02

	Carcinogenicity Studies		

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
Desk Copy	Request for Blank CRF, Protocol and Protocol Amendments for LAM-IV-307	To: Dr. R. Shibuya Fm: S. Krishnan	07/25/02
RegCon	Request for ninety-day meeting	To: D. Henton Fm: S. Krishnan	07/11/02
006	General Correspondence – Ninety-day Meeting Request	To: Dr. Throckmorton Fm: S. Krishnan	07/11/02
RegCon	To enquire about the progress of the NDA review.	To: Dr. J. C. Pelayo Fm: S. Krishnan	07/02/02
Electronic File	Request for electronic copy of preclinical data sets for carcinogenicity studies in mice [SPD/87/C and SPD/88/C]), information regarding criteria test results in the in vitro chromosomal aberration studies and the historical control data for gene mutation and chromosomal aberration frequency in the CHO cells, and bone expert report. (note to file: audit 4/16/03-no paper or elec copy in work file)	To: Electronic Document Room Fm: S. Krishnan	06/28/02
E-Mail	Per RegCon requested dated 06/26/02 for Information on CMC: Lot Numbers of Drug Substance and Drug Product that were and will be tested by TGA and ICP at Quintiles respectively. And the Certificate of Analysis of Drug Substance lots tested at Quintiles, Kansas and included in NDA. (note to file: email is customarily filed in Correspondence log only)	To: S. Berryman Fm: S. Krishnan	06/27/02
Response to Div. Sci. Inv.	Response to FDA Request	To: Dr. R. Shibuya Fm: S. Krishnan	06/25/02
Desk Copy	Request for 1 additional copy of Vol. 1.1 & Vol. 1.2	To: Dr. Throckmorton Fm: S. Krishnan	06/21/02
005	General Correspondence – NonClinical Pharmacology and Toxicology (additional study reports for SPD0130, R00081-LAM-IIIQ and R00182-LAM-IIIQ)	To: Dr. Throckmorton Fm: S. Krishnan	06/19/02
004	General Correspondence (Bone Expert Report)	To: Dr. Throckmorton Fm: S. Krishnan	06/14/02

NDA SUBMISSION LOGBOOK

NDA No. 21-468 **Title: FOSRENOL™ (Lanthanum Carbonate Hydrate)**

Submission to FDA (continued)

Submission No.	Type of Submission	To/From	Date
Desk Copy	**Resubmission of electronic copy** of preclinical data sets for carcinogenicity studies in mice [SPD/87/C and SPD/88/C]), information regarding criteria test results in the in vitro chromosomal aberration studies and the historical control data for gene mutation and chromosomal aberration frequency in the CHO cells, and bone expert report.	To: Dr. Xavier Joseph (PharmTox Reviewer) Fm: S. Krishnan	06/14/02
Fax	CMC documentation pages of original NDA pertaining to testing performed at Quintiles in Kansas City. (note to file: audit 4/16/03, Missing in file)	To: Shirley Berryman Fm: S. Krishnan	06/13/02
Desk Copy	Request for 1 additional copy of Vol. 1.1	To: Dr. Throckmorton Fm: S. Krishnan	06/12/02
003	General Correspondence (Per regcon request dated 6/3/02 for additional CMC information on manufacturing and testing contact info, clarify ID test performed on HCl, and update flow diagram to reflect use of Nitrogen).	To: Dr. Throckmorton Fm: S. Krishnan	06/07/02
Desk Copy	Request for 2 additional copies of CMC Section (Vol. 1.3 ,1.4)	To: Dr. Throckmorton Fm: S. Krishnan	06/04/02
002	General Correspondence (Per regcon request dated 5/13/02 for information regarding criteria test results in the in vitro chromosomal aberration studies and the historical control data for gene mutation and chromosomal aberration frequency in the CHO cells).	To: Dr. Throckmorton Fm: S. Krishnan	05/22/02
001	General Correspondence (Per regcon request dated 5/13/02 for additional copies of draft package insert, and e-copy of preclinical data sets for carcinogenicity studies in mice [SPD/87/C and SPD/88/C]).	To: Dr. Throckmorton Fm: S. Krishnan	05/21/02
Volume 1.1-1.762	Original NDA Submission (762 acco binders on shelf) (note to file: audit 4/16/2003 – volume #117 out to Y. Zhang on 2/25/03).	To: CDR Fm: R. Lilley	04/30/02

NDA SUBMISSION LOGBOOK

NDA No. 21-468 FOSRENOL® (Lanthanum Carbonate)

Submissions to FDA

Submission No.	Type of Submission	To/From	Date
095	General Correspondence: Final Draft Labels and Labeling	To: Dr. Stockbridge Fm: L. Wittmer	10/20/04
094	General Correspondence: Request for Type C Meeting	To: Dr. Stockbridge Fm: L. Wittmer	10/21/04
093	General Correspondence: Final Draft Labeling (revised)	To: EDR Fm: D. Ahern	10/14/04
092	General Correspondence: Final Draft Labeling	To: EDR Fm: D. Ahern	10/11/04
091	CMC Amendment	To: Dr. Stockbridge Fm: L. Wittmer	10/1/04
090	General Correspondence: CMC	To: Dr. Stockbridge Fm: L. Wittmer	9/10/04
089	CMC Amendment: Updated lanthanum carbonate specification and test methods	To: Dr. Stockbridge Fm: L. Wittmer	9/2/04
088	General Correspondence: Meeting Minutes (CMC and Biopharm Teleconference 27-Aug-04)	To: Dr. Stockbridge Fm: L. Wittmer	9/2/04
087	General Correspondence: Pharmacovigilence Risk Management Plan Supplement	To: Dr. Stockbridge and Desk Copy D. Hinton Fm: L. Wittmer	9/1/04
086	Response to Request for Information – CMC Section (Cumulative Revisions)	To: Dr. Stockbridge and FIELD OFFICE COPY Fm: L. Wittmer	8/18/04
085	Response for Request for Information (Revised Labels and Labeling)	To: FDA Central Document Room/EDR Fm: L. Wittmer	8/11/04
084	General Correspondence: CMC	To: Dr. Stockbridge Fm: L. Wittmer	8/06/04
083	Response to Request for Information (Updated current formulation specs)	To: Dr. Stockbridge Fm: L. Wittmer	7/26/04
082	Response to Request for Information (Dissolution data and updated specifications; Pharmacodynamic equivalence – responses to inspection items; Sample bottle labels)	To: Dr. Stockbridge Fm: L. Wittmer	7/23/04
081	Pathology report	To: Dr. Stockbridge Fm: L. Wittmer	7/12/04
080	CMC Amendment	To: Dr. Stockbridge Fm: L. Wittmer	7/12/04

079	CMC Amendment	To: Dr. Stockbridge Fm: L. Wittmer	7/8/04
078	Table outlining studies in which healthy volunteer have received lanthanum	To: Dr. Stockbridge Fm: L. Wittmer	7/6/04
077	General Correspondence: Response to FDA Request for Information	To: Dr. Stockbridge Fm: L. Wittmer	6/24/04
076	General Correspondence: Meeting Summary from 17-Jun-2004	To: Dr. Stockbridge Fm: L. Wittmer	6/21/04
075	Briefing Package for FDA Meeting on 11-Jun-2004	To: Dr. Stockbridge Fm: L. Wittmer	6/2/04
074	General Correspondence: Request for Information (Safety Update for LAM-IV-307)	To: Dr. Stockbridge Fm: L. Wittmer	6/1/04
073	CMC Amendment	To: Dr. Stockbridge Fm: L. Wittmer	5/28/04
071	General Correspondence: Bioanalytical Reports	To: Dr. Throckmorton Fm: L. Wittmer	5/6/04
072	General Correspondence: Response to Information Request Letter	To: Dr. Throckmorton Fm: L. Wittmer	5/5/04
070	Response to Request for Information (CMC)	To: Dr. Throckmorton Fm: L. Wittmer	4/1/04
069	Response to Request for Information (AE)	To: Dr. Throckmorton Fm: L. Wittmer	4/1/04
068	Response to FDA Request for Information	To: Dr. Throckmorton Fm: L. Wittmer	3/22/04
067	Resubmission of Electronic Component of New Drug Application	To: Dr. Throckmorton Fm: L. Wittmer	2/2/04
066	Resubmission of New Drug Application	To: Dr. Throckmorton Fm: L. Wittmer	1/26/04
065	Clinical Amendment: Final Clinical Study Report SPD405-116	To: Dr. Throckmorton Fm: L. Wittmer	11/25/03
064	Pre-resubmission Briefing Package (to be held on 3-Dec-2003)	To: Dr. Throckmorton Fm: L. Wittmer	11/10/03
063	General Correspondence: Copy of USAN Letter	To: Dr. Throckmorton Fm: L. Wittmer	9/5/03
062	General Correspondence	To: Dr. Throckmorton Fm: L. Wittmer	8/27/03
061	General Correspondence: Meeting summary from 7-Aug-03 FDA meeting	To: Dr. Throckmorton Fm: L. Wittmer	8/27/03
060	Meeting Information Package (Revision)	To: Dr. Throckmorton Fm: L. Wittmer	8/4/03
059	Meeting Information Package (CMC meeting on 7-Aug-03)	To: Dr. Throckmorton Fm: L. Wittmer	7/21/03
058	General Correspondence: Meeting summary from 3-Jul-03 FDA meeting	To: Dr. Throckmorton Fm: L. Wittmer	7/14/03

057	General Correspondence: Meeting summary from 26-Jun-03 CMC teleconference	To: Dr. Throckmorton Fm: L. Wittmer	7/14/03
056	General Correspondence: Request for Type C Meeting	To: Dr. Throckmorton Fm: L. Wittmer	6/25/03
055	General Correspondence – CMC	To: Dr. Throckmorton Fm: L. Wittmer	5/2/03
054	General Correspondence – Request for Feedback	To: Dr. Throckmorton Fm: L. Wittmer	5/2/03
053	General Correspondence – CMC	To: Dr. Throckmorton Fm: L. Wittmer	4/24/03
052	General Correspondence – CMC	To: Dr. Throckmorton Fm: L. Wittmer	4/11/03
051	General Correspondence – Meeting Summary (27 March 03)	To: Dr. Throckmorton Fm: L. Wittmer	4/10/03
050	General Correspondence – CMC Response to FDA Questions	To: Dr. Throckmorton Fm: L. Wittmer	3/31/03
049	General Correspondence - Pre Meeting Briefing Documents	To: Dr. Throckmorton Fm: M. McLoudrey	3/24/03
048	General Correspondence - Notice of Intent to File an Amendment and Request for Teleconference in Response to FDA Approvable Action Letter Dated 02/28/03	To: Dr. Throckmorton Fm: M. McLoudrey	3/07/03
047	General Correspondence – Response to Statistical Reviewer's Request for Information	To: Dr. Throckmorton Fm: G. Miller	2/12/03
046	General Correspondence: Response to CMC Information Request (reference to conversation on 1/15/03 between Ms. Hinton and Dr. Wittmer)	To: Dr. Throckmorton Fm: L. Wittmer	1/28/03
045	General Correspondence: Response to Statistical Reviewer's Request	To: Dr. Throckmorton Fm: L. Wittmer	1/27/03
044	General Correspondence: Response to Medical Reviewer's Request	To: Dr. Throckmorton Fm: L. Wittmer	1/23/03
043	General Correspondence: Response to Statistical Reviewer's and Medical Reviewer's Requests	To: Dr. Throckmorton Fm: L. Wittmer	12/23/02
042	General Correspondence – Clinical Information	To: Dr. Throckmorton Fm: L. Wittmer	12/20/02
041	General Correspondence – Response to CMC Reviewer's Request for Information	To: Dr. Throckmorton Fm: L. Wittmer	12/20/02
040	General Correspondence – Meeting Minutes (from the CMC teleconference held on December 12, 2002)	To: Dr. Throckmorton Fm: L. Wittmer	12/18/02

039	General Correspondence – Response to Statistical Reviewer's Request	To: Dr. Throckmorton Fm: L. Wittmer	12/16/02
038	Amendment – Chemistry Manufacturing and Controls	To: Dr. Throckmorton Fm: L. Wittmer	12/13/02
037	Electronic Submission - Fosrenol Bottle Labels for the 250 and 500 mg tablets	To: Dr. Throckmorton Fm: L. Wittmer	12/13/02
036	General Correspondence-Meeting Minutes from Dec 3	To: Dr. Throckmorton Fm: L. Wittmer	12/06/02
035	General Correspondence – CMC Information	To: Dr. Throckmorton Fm: L. Wittmer	11/27/02
034	Electronic File (Proposed package insert)	To: Central Doc Room Fm: L. Wittmer	11/27/02
033	General Correspondence – CMC Information	To: Dr. Throckmorton Fm: L. Wittmer	11/27/02
032	Electronic File – SAS Program for study LAM-IV-307	To: Central Doc Room Fm: L. Wittmer	11/22/02
031	Electronic File – ECG datasets for studies 204, 205, 302 and 308 - ECG dataset for study 307 with changes as requested by Biostat reviewer - Results of ECG for 307	To: Central Doc Room Fm: L. Wittmer	11/22/02
030	General Correspondence – Clinical Information	To: Dr. Throckmorton Fm: L. Wittmer	11/21/02
029	Electronic File (Response to FDA Request for Additional Clinical Data)	To: Central Document Room Fm: L. Wittmer	11/15/02
028	Electronic File (Response to FDA Request)	To: Central Document Room Fm: R. Lilley	11/11/02
027	General Correspondence – Additional CMC Information and response to questions raised at 90-day meeting	To: Dr. Throckmorton Fm: R. Lilley	11/04/02
026	General Correspondence – Response to FDA Request	To: Dr. Throckmorton Fm: R. Lilley	11/01/02
025	General Correspondence – Response to Preclinical Questions at teleconference on 10/23/02 with Dr. Joseph	To: Dr. Throckmorton Fm: R. Lilley	10/28/02
024	General Correspondence – Response to Preclinical Request	To: Dr. Throckmorton Fm: R. Lilley	10/24/02
023	General Correspondence – Response to FDA Question	To: Dr. Throckmorton Fm: R. Lilley	10/22/02
022	General Correspondence – Response to FDA Request	To: Dr. Throckmorton Fm: S. Krishnan	10/08/02
021	General Correspondence – Response to FDA Request	To: Dr. Throckmorton Fm: S. Krishnan	10/03/02

020	General Correspondence – Response to FDA Request	To: Dr. Throckmorton Fm: S. Krishnan	09/25/02
019	General Correspondence – CMC	To: Dr. Throckmorton Fm: S. Krishnan	09/18/02
018	General Correspondence – Response to FDA Request	To: Dr. Throckmorton Fm: S. Krishnan	09/16/02
017	General Correspondence – Ninety Day Meeting Minutes from 9/5/02 meeting	To: Dr. Throckmorton Fm: S. Krishnan	09/13/02
016	Resubmission of Electronic Files for Four Month Safety Update – Integrated Summary of Safety	To: Central Document Room Fm: S. Krishnan	09/10/02
015	General Correspondence – Response to FDA Request (NonClinical Pharmacology and Toxicology for statistical analysis report)	To: Dr. Throckmorton Fm: S. Krishnan	08/30/02
014	Electronic Files for Four Month Safety Update – Integrated Summary of Safety	To: Dr. Throckmorton Fm: S. Krishnan	08/30/02
013	Four Month Safety Update – Integrated Summary of Safety	To: Dr. Throckmorton Fm: S. Krishnan	08/30/02
012	General Correspondence – CMC	To: Dr. Throckmorton Fm: S. Krishnan	08/29/02
Letter	General Correspondence – Change of Company Address	To: Dr. Throckmorton Fm: S. Krishnan	08/29/02
011	General Correspondence – Briefing Package (Ninety Day Meeting on 9/5/02)	To: Dr. Throckmorton Fm: S. Krishnan	08/27/02
010	General Correspondence – Response to FDA request	To: Dr. Throckmorton Fm: S. Krishnan	08/27/02
009	General Correspondence – Response to FDA Request (Nonclinical Pharmacology and Toxicology)	To: Dr. Throckmorton Fm: S. Krishnan	08/14/02
008	Resubmission of Electronic Files for Study Reports 202, 204, 301, 302, 307 and Carcinogenicity Studies	To: Electronic Doc. Rm Fm: S. Krishnan	08/05/02
007	General Correspondence- Response to FDA Request for Additional Information	To: Dr. Throckmorton Fm: S. Krishnan	07/30/02
006	General Correspondence – Ninety-day Meeting Request	To: Dr. Throckmorton Fm: S. Krishnan	07/11/02
005	General Correspondence – NonClinical Pharmacology and Toxicology	To: Dr. Throckmorton Fm: S. Krishnan	06/19/02
004	General Correspondence	To: Dr. Throckmorton Fm: S. Krishnan	06/14/02

003	General Correspondence (FDA request for additional CMC information on manufacturing and testing contact info)	To: Dr. Throckmorton Fm: S. Krishnan	06/07/02
002	General Correspondence (FDA request for information)	To: Dr. Throckmorton Fm: S. Krishnan	05/22/02
001	General Correspondence (FDA request for additional copies of draft package insert, and e-copy of preclinical data sets)	To: Dr. Throckmorton Fm: S. Krishnan	05/21/02
000 **(Volume 1.1-1.762)**	Original NDA Submission	To: Central Document Room Fm: R. Lilley	04/30/02

IND SUBMISSION LOGBOOK

IND 55,054 Lanthanum Carbonate (FOSRENOL®)

Submissions to FDA

IND Serial No.	Description of Document	To/From	Date
170	Other (Change of Company Name/Address)	To: Dr. Stockbridge Fm: C. LaPree	11/18/04
169	Protocol Amendment: New Investigator (Updated Form 1572 for SPD405-309)	To: Dr. Stockbridge Fm: L. Wittmer	11/16/04
168	Protocol Amendment: New Protocol (SPD405-310)	To: Dr. Stockbridge Fm: D. Ahern	11/2/04
167	Follow-up to 15-Day Safety Report - Protocol SPD405.309	To: Dr. Throckmorton Fm: L. Wittmer	8/11/04
166	Protocol Amendment: New Investigator (SPD405-312)	To: Dr. Stockbridge Fm: L. Wittmer	7/27/04
165	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: L. Wittmer	6/18/04
164	Follow-up to 15-Day Safety Report - Protocol SPD405.309	To: Dr. Throckmorton Fm: L. Wittmer	6/8/04
163	15-Day Safety Report - Protocol SPD405.309	To: Dr. Throckmorton Fm: L. Wittmer	5/18/04
162	Annual Report (Reporting period 2/14/03-2/13/04)	To: Dr. Throckmorton Fm: L. Wittmer	4/20/04
161	Protocol Amendment: Change in Protocol (SPD405-312, Amendment 1)	To: Dr. Throckmorton Fm: L. Wittmer	4/15/04
160	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: L. Wittmer	3/22/04
159	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: L. Wittmer	3/22/04
158	New Protocol (SPD405-312) and CMC Amendment	To: Dr. Throckmorton Fm: L. Wittmer	12/29/03
157	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: L. Wittmer	12/17/03
156	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: L. Wittmer	12/17/03
155	Protocol Amendment: Investigator Update	To: Dr. Throckmorton Fm: L. Wittmer	12/17/03
154	Protocol Amendment: Investigator Update	To: Dr. Throckmorton Fm: L. Wittmer	12/17/03
153	Protocol Amendment: Change in Protocol (SPD405.309, Amendment 2)	To: Dr. Throckmorton Fm: L. Wittmer	11/13/03
152	Clinical Study Report LAM-IV-205, Amendment 1	To: Dr. Throckmorton Fm: L. Wittmer	11/07/03
151	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: L. Wittmer	09/09/03
150	Investigator's Brochure (Version 10)	To: Dr. Throckmorton Fm: L. Wittmer	09/09/03

149	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: L. Wittmer	07/09/03
148	Annual Report (Reporting period 2/14/02-2/13/03)	To: Dr. Throckmorton Fm: L. Wittmer	06/11/03
147	Protocol Amendment: Change in Protocol (LAM-IV-307, Amendment 8)	To: Dr. Throckmorton Fm: L. Wittmer	05/23/03
146	General Correspondence: Protocol Synopsis for Comment (SPD405-312)	To: Dr. Throckmorton Fm: L. Wittmer	04/25/03
145	Protocol Amendment: New Investigator Update	To: Dr. Throckmorton Fm: M. McLoudrey	03/28/03
144	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: M. McLoudrey	03/28/03
143	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: M. McLoudrey	02/03/03
142	Protocol Amendment: New Investigator Update	To: Dr. Throckmorton Fm: L. Wittmer	01/02/03
141	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: L. Wittmer	01/02/03
140	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: R. Lilley	11/08/02
139	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: S. Krishnan	10/10/02
138	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: S. Krishnan	10/04/02
137	Change of Company Address	To: Dr. Throckmorton Fm: R. Lilley	08/29/02
136	Annual Report (2/01-2/02)	To: Dr. Throckmorton Fm: S. Krishnan	07/17/02
135	Protocol Amendments: New Protocol and Change in Protocol (Amendment 1) to SPD 405.309	To: Dr. Throckmorton Fm: S. Krishnan	6/14/02
134	Follow-up to 15-Day Safety Report	To: Dr. Lipicky Fm: Rick Lilley	6/6/02
133	Other-Request for Waiver of Pediatric Studies (for Fosrenol NDA 21-468)	To: Dr. Throckmorton Fm: S. Krishnan	4/26/02
132	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: S. Krishnan	3/19/02
131	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: S. Krishnan	3/5/02
130	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: S. Krishnan	3/5/02
129	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: S. Krishnan	3/4/02
128	Protocol Amendment: New Investigator	To: Dr. Throckmorton Fm: S. Krishnan	3/4/02
127	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Krishnan	3/4/02
126	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Krishnan	2/18/02

125	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Krishnan	2/13/02
124	Notice of Termination of Clinical Investigator	To: Dr. Lipicky Fm: S. Krishnan	2/11/02
123	Follow-up to 15-Day Safety Report	To: Dr. Lipicky Fm: S. Krishnan	1/29/02
122	Follow-up to 15-Day Safety Report	To: Dr. Lipicky Fm: S. Krishnan	1/14/02
121	15-Day Safety Report (LAM-IV-307)	To: Dr. Lipicky Fm: S. Krishnan	1/3/02
120	Information Amendment: Clinical (Revised IB)	To: Dr. Lipicky Fm: S. Krishnan	12/17/01
119	Protocol Amendment: Change in Protocol (LAM-IV-307 Amend #6 & #7)	To: Dr. Lipicky Fm: S. Krishnan	12/17/01
118	General Correspondence (Meeting Minutes from 10/23/01)	To: Dr. Lipicky Fm: S. Krishnan	11/13/01
117	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Krishnan	11/12/01
116	General Correspondence: Pre-NDA Clinical/Nonclinical Meeting Minutes from 9/18/01	To: Dr. Lipicky Fm: S. Krishnan	10/4/01
115	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Krishnan	10/2/01
114	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Krishnan	9/28/01
113	General Correspondence: Follow-up information from the Pre-NDA meeting	To: Dr. Lipicky Fm: S. Krishnan	9/19/01
112	General Correspondence: Pre-NDA Briefing Information Package	To: Dr. Lipicky Fm: S. Krishnan	9/4/01
111	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Krishnan	7/25/01
110	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Krishnan	7/19/01
109	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Krishnan	7/16/01
108	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Krishnan	7/19/01
107	General Correspondence: Request for Type B Meeting	To: Dr. Lipicky Fm: S. Krishnan	7/6/01
106	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Krishnan	6/28/01
105	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Krishnan	6/28/01
104	Follow-up to 15-Day Safety Report	To: Dr. Lipicky Fm: S. Krishnan	6/27/01
103	Protocol Amendment: Change in Protocol (307 Amend #5)	To: Dr. Lipicky Fm: S. Krishnan	6/11/01
102	Annual Report (2/00-2/01)	To: Dr. Lipicky Fm: S. Krishnan	5/29/01

101	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Krishnan	5/17/01
100	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Krishnan	5/4/01
099	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	4/23/01
098	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	3/26/01
097	15-Day Safety Report (LAM-IV-301)	To: Dr. Lipicky Fm: T. Martin	3/12/01
096	Protocol Amendment: Change in Protocol (307 Amend #4)	To: Dr. Lipicky Fm: T. Martin	3/5/01
095	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	3/5/01
094	15-Day Safety Report (LAM-IV-307)	To: Dr. Lipicky Fm: T. Martin	3/5/01
093	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	2/15/01
092	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	2/2/01
091	Protocol Amendment: Change in Protocol (LAM-IV-111 Amend #2)	To: Dr. Lipicky Fm: T. Martin	1/31/01
090	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	1/17/01
089	General Correspondence: Protocol LAM-IV-303	To: Dr. Lipicky Fm: T. Martin	1/15/01
088	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	1/10/01
087	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	1/8/01
086	General Correspondence: Draft Protocol LAM-IV-113	To: Dr. Lipicky Fm: T. Martin	1/4/01
085	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	1/3/01
084	CMC Amendment to the IND Application	To: Dr. Lipicky Fm: R. Kishore	11/27/00
083	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	11/21/00
082	Protocol Amendment: Change in Protocol (111 Amend #1)	To: Dr. Lipicky Fm: T. Martin	11/20/00
081	Follow-up #2 to 15-Day Safety Report (Protocol LAM-IV-307)	To: Dr. Lipicky Fm: T. Martin	11/17/00
080	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	11/8/00
079	Protocol Amendment: New Protocol (LAM-IV-111)	To: Dr. Lipicky Fm: T. Martin	10/19/00
078	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	10/19/00
077	15-Day Safety Report Protocol (LAM-IV-303)	To: Dr. Lipicky Fm: T. Martin	10/17/00
076	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	10/10/00

075	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	10/2/00
074	Annual Report (2/99-2/00)	To: Dr. Lipicky Fm: T. Martin	9/28/00
073	General Correspondence: Trade Name Evaluation	To: Dr. Lipicky Fm: T. Martin	9/28/00
072	Protocol Amendment: New Protocol (LAM-IV-112)	To: Dr. Lipicky Fm: T. Martin	9/28/00
071	General Correspondence (ongoing program of IND and ensure the parameters chosen are acceptable)	To: Dr. Lipicky Fm: T. Martin	9/22/00
070	Information Amendment: Tox Report	To: Dr. Lipicky Fm: T. Martin	9/19/00
069	General Correspondence (Bone assessments, response to FDA questions)	To: Dr. Lipicky Fm: T. Martin	8/22/00
068	Follow-up 15-Day Safety Report	To: Dr. Lipicky Fm: T. Martin	8/18/00
067	Protocol Amendment: Change in Protocol (308 Amend #1 & 2)	To: Dr. Lipicky Fm: T. Martin	8/11/00
066	Protocol Amendment: Change in Protocol (307 Amend #2 & 3)	To: Dr. Lipicky Fm: T. Martin	8/11/00
065	15-Day Safety Report	To: Dr. Lipicky Fm: T. Martin	7/31/00
064	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	7/28/00
063	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	6/26/00
062	General Correspondence	To: Dr. Lipicky Fm: T. Martin	6/7/00
061	15-Day Safety Report	To: Dr. Lipicky Fm: T. Martin	6/5/00
060	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	5/10/00
059	Follow-up 15-Day Safety Report	To: Dr. Lipicky Fm: T. Martin	5/8/00
058	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	4/27/00
057	General Correspondence (revised draft LAM-IV-111)	To: Dr. Lipicky Fm: T. Martin	4/17/00
056	General Correspondence	To: Dr. Lipicky Fm: T. Martin	4/4/00
055	15-Day Safety Report	To: Dr. Lipicky Fm: T. Martin	3/29/00
054	15-Day Safety Report	To: Dr. Lipicky Fm: T. Martin	3/20/00
053	General Correspondence (draft protocol LAM-IV-111)	To: Dr. Lipicky Fm: T. Martin	3/20/00
052	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	3/17/00
051	15-Day Safety Report	To: Dr. Lipicky Fm: T. Martin	3/15/00

050	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	3/1/00
049	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	2/17/00
048	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	2/4/00
047	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	1/12/00
046	General Correspondence: Amendment to IB	To: Dr. Lipicky Fm: S. Geroux	1/6/00
045	Protocol Amendment: New Protocol (LAM-IV-308)	To: Dr. Lipicky Fm: S. Geroux	12/21/99
044	Follow-up 15-Day Safety Report	To: Dr. Lipicky Fm: T. Martin	12/21/99
043	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	12/16/99
042	General Correspondence (IC)	To: Dr. Lipicky Fm: S. Geroux	12/14/99
041	Follow-up 15-Day Safety Report	To: Dr. Lipicky Fm: S. Geroux	12/3/99
040	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	11/18/99
039	Information Amendment: Pharm/Tox	To: Dr. Lipicky Fm: S. Geroux	11/16/99
038	Information Amendment: Clinical (Final study report LAM-IV-204)	To: Dr. Lipicky Fm: S. Geroux	10/27/99
037	General Correspondence	To: Dr. Lipicky Fm: S. Geroux	10/20/99
036	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	10/19/99
035	Protocol Amendment: Change in Protocol (LAM-IV-307 Amend #1)	To: Dr. Lipicky Fm: S. Geroux	10/18/99
034	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	10/7/99
033	Protocol Amendment: New Protocol (LAM-IV-302)	To: Dr. Lipicky Fm: S. Geroux	9/28/99
032	General Correspondence (Response to FDA request for information)	To: E. Fromm Fm: S. Geroux	9/8/99
031	Follow-up 15-Day Safety Report	To: Dr. Lipicky Fm: S. Geroux	8/30/99
030	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	8/30/99
029	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: T. Martin	8/19/99
028	General Correspondence (copy of telecon on 8/12/99)	To: Dr. Lipicky Fm: T. Martin	8/17/99
027	General Correspondence (Response to FDA request for information) IB Version 8, IC for 205 & 307	To: Dr. Lipicky Fm: T. Martin	8/17/99

026	15-Day Safety Report	To: Dr. Lipicky Fm: S. Geroux	8/17/99
025	15-Day Safety Report	To: Dr. Lipicky Fm: S. Geroux	8/10/99
024	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	8/9/99
023	15-Day Safety Report	To: Dr. Lipicky Fm: S. Geroux	8/3/99
022	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	7/30/99
021	Protocol Amendment: New Protocol (LAM-IV-110) and Change in Protocol (LAM-IV-109 Amend #1)	To: Dr. Lipicky Fm: S. Geroux	7/27/99
020	Protocol Amendment: New Protocol (LAM-IV-302)	To: Dr. Lipicky Fm: S. Geroux	7/20/99
019	Protocol Amendment: New Protocol (LAM-IV-307) and New Investigators	To: Dr. Lipicky Fm: S. Geroux	7/20/99
018	15-Day Safety Report	To: Dr. Lipicky Fm: S. Geroux	7/9/99
Regcon	7-Day Safety Report	To: Colleen LoCicero & Dr. Pelayo	6/28/99
017	General Correspondence (Press Release)	To: Dr. Lipicky Fm: T. Martin	6/24/99
016	General Correspondence (Draft Protocol LAM-IV-307)	To: Dr. Lipicky Fm: S. Geroux	6/16/99
015	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	5/14/99
014	End of Phase II Meeting Clinical Briefing Pack	To: Dr. Lipicky Fm: S. Geroux	4/27/99
013	End of Phase II Meeting CMC Briefing Pack	To: Dr. Lipicky Fm: S. Geroux	4/26/99
012	Information Amendment: Response to FDA's request for Information	To: Dr. Lipicky Fm: S. Geroux	4/19/99
011	Annual Report (2/98-2/99)	To: Dr. Lipicky Fm: S. Geroux	4/19/99
010	Protocol Amendment: Change in Protocol (LAM-IV-205 Amend #2 and #3)	To: Dr. Lipicky Fm: S. Geroux	3/22/99
009	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	3/8/99
008	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	2/2/99
007	Protocol Amendment: Change in Protocol (LAM-IV-204 Amend #2, LAM-IV-205 Amend #1)	To: Dr. Lipicky Fm: S. Geroux	10/5/98
006	Protocol Amendment: New Protocol (LAM-IV-205)	To: Dr. Lipicky Fm: T. Martin	9/9/98
005	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	8/19/98

004	Protocol Amendment: New Investigator	To: Dr. Lipicky Fm: S. Geroux	7/31/98
003	Protocol Amendment: Change in Protocol (LAM-IV-204 Amend #1) and New Investigator	To: Dr. Lipicky Fm: S. Geroux	5/6/98
002	General Correspondence (Request for alternative frequency reporting of AE's)	To: Dr. Lipicky Fm: T. Martin	4/16/98
001	Information Amendment (Mutagenicity Reports)	To: Dr. Lipicky Fm: S. Geroux	2/5/98
000	Initial IND Submission	To: Dr. Lipicky Fm: E. Rudnic	1/14/98
Pre-IND	Pre-IND Meeting minutes	To: Dr. Lipicky Fm: S. Geroux	7/23/97
Letter	Pre-IND Meeting Request	To: Dr. Lipicky Fm: S. Geroux	7/07/97

Proprietary Name Search Results from "OB_Rx" table for query on "FOSRENOL."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
021468		No	LANTHANUM CARBONATE	TABLET, CHEWABLE; ORAL	250MG	FOSRENOL	SHIRE PHARM
021468		Yes	LANTHANUM CARBONATE	TABLET, CHEWABLE; ORAL	500MG	FOSRENOL	SHIRE PHARM

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Patent and Exclusivity Search Results from query on Appl No 021468 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021468	001	5968976	MAR 19,2016		Y	U-613

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021468	001	NCE	OCT 26,2009

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1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
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